SPECIAL COLLECTOR'S EDITION

SCIENTIFIC AMERICAN

SPRING 2015

Secrets of STAYING YOUNG

The science of healthy aging

INSIDE

- Why We Age
- Stay Smart, Boost Energy
- How Exercise Helps Memory
- The Regenerating Brain
- Lessons from the Oldest Old

© 2015 Scientific American

SCIENTIFIC AMERICAN SPECIAL COLLECTOR'S EDITION SECRETS OF STAYING YOUNG VOLUME 24, NUMBER 1

AARP Real Possibilities with

Staying Sharp

A HEALTHY BODY LEADS TO A **HEALTHY MIND.**

Keeping Fit is just one of the five pillars of AARP's holistic approach to brain health. The Staying Sharp membership helps you stay active, which keeps your brain engaged and challenged. As a member, you'll be able to find information and tips to increase your activity level and improve brain health.

Join now at **aarp.org/joinstayingsharp**

SCIENTIFIC AMERICAN™
ESTABLISHED 1845

Secrets of Staying Young is published by the staff of Scientific American, with project management by:

EDITOR IN CHIEF AND SENIOR VICE PRESIDENT
Mariette DiChristina
EXECUTIVE EDITOR **Fred Guterl**
MANAGING EDITOR **Ricki L. Rusting**
ISSUE EDITOR **Dawn Stover**
DESIGN DIRECTOR **Michael Mrak**
ISSUE DESIGNER **Lawrence R. Gendron**
PHOTOGRAPHY EDITOR **Monica Bradley**
PHOTO RESEARCHER **Liz Tormes**
MANAGING PRODUCTION EDITOR **Richard Hunt**
SENIOR PRODUCTION EDITOR **Michelle Wright**
COPY DIRECTOR **Maria-Christina Keller**
SENIOR COPY EDITOR **Daniel C. Schlenoff**
COPY EDITOR **Aaron Shattuck**
EDITORIAL ADMINISTRATOR **Avonelle Wing**
SENIOR SECRETARY **Maya Harty**
SENIOR PRODUCTION MANAGER
Christina Hippeli
ADVERTISING PRODUCTION MANAGER
Carl Cherebin
PREPRESS AND QUALITY MANAGER
Silvia De Santis
CUSTOM PUBLISHING MANAGER
Madelyn Keyes-Milch
PRODUCTION COORDINATOR **Lisa Headley**

PRESIDENT
Steven Inchcoombe
EXECUTIVE VICE PRESIDENT
Michael Florek
VICE PRESIDENT AND ASSOCIATE PUBLISHER, MARKETING AND BUSINESS DEVELOPMENT
Michael Voss
DIRECTOR, INTEGRATED MEDIA SALES
Stan Schmidt
ASSOCIATE VICE PRESIDENT, BUSINESS DEVELOPMENT
Diane McGarvey
VICE PRESIDENT, GLOBAL MEDIA ALLIANCES
Jeremy A. Abbate
VICE PRESIDENT, CONSUMER MARKETING
Christian Dorbandt
DIRECTOR, INTERNATIONAL DIGITAL DEVELOPMENT
Richard Zinken
ASSOCIATE CONSUMER MARKETING DIRECTOR
Catherine Bussey
E-COMMERCE MARKETING MANAGER
Evelyn Veras
MARKETING AND CUSTOMER SERVICE COORDINATOR
Christine Kaelin
SALES DEVELOPMENT MANAGER **David Tirpack**
PROMOTION MANAGER **Diane Schube**
PROMOTION ART DIRECTOR **Maria Cruz-Lord**
MARKETING RESEARCH DIRECTOR **Rick Simone**
ONLINE MARKETING PRODUCT MANAGER
Zoya Lysak
CORPORATE PR MANAGER **Rachel Scheer**
SENIOR INTEGRATED SALES MANAGERS
Jay Berfas, Matt Bondlow
SALES REPRESENTATIVE **Chantel Arroyo**
SENIOR ADMINISTRATOR, EXECUTIVE SERVICES
May Jung
CUSTOM PUBLISHING EDITOR **Lisa Pallatroni**
RIGHTS AND PERMISSIONS MANAGER
Karin M. Tucker

COVER PHOTOGRAPH BY GETTY IMAGES: SEBASTIEN FEVAL *Getty Images (Marchand)*:
SCIENTIFIC AMERICAN IS A TRADEMARK OF SCIENTIFIC AMERICAN, INC., USED WITH PERMISSION

INTRODUCTION

To Your Health!

If you read the headlines (or the obituaries), you know that heart disease, cancer, diabetes and other ailments send too many people to an early grave. But some individuals both escape those scourges and remain in good condition well past the average age of death. Just look at Robert Marchand (*seen above*), the French cyclist who last year beat his own world record in the 100-and-over class by riding almost 27 kilometers in one hour. He was 102 years old.

Marchand and others like him are part of the surprisingly fit cohort known as "the oldest old," described in an article by geriatrician Thomas T. Perls (*page 100*). The latest studies of people in their 90s and beyond reveal that they are often as vigorous as much younger people and are able to maintain their good health—mental and physical—for many decades. Investigators are studying this group in the hope of finding helpful insights for the general population.

Can we live forever? Not likely. But as British aging expert Thomas Kirkwood writes in "Why Can't We Live Forever?" (*page 12*), science provides an abundance of clues about how we can live longer and, more important, stave off infirmities for as long as possible.

Exercise is proving to be a key factor, as several authors in this collection emphasize. Changes as simple as standing instead of sitting can have enormous benefits for weight loss and metabolism (*page 54*). Researchers are also exploring strategies such as intermittent fasting (*page 56*) and are punching holes in once accepted theories about the anti-aging effects of antioxidants and vitamins (*page 20*).

A couple of articles focus on new ways to slow age-related forgetfulness (*page 34* and *page 36*). In some cases, steering clear of medicines that can affect memory does the trick (*page 38*). There is plenty of good news on the drug front, though. Scientists are working on interventions for detecting and tackling Alzheimer's disease before symptoms appear (*page 66* and *page 74*). They are experimenting with stem cells as a way to repair brain damage from Parkinson's disease and to treat diabetes and cancer (*page 76*). Moreover, they are investigating drugs that would slow aging-related processes at the cellular level, as science writer David Stipp investigates in "A New Path to Longevity" (*page 86*).

Will these techniques for staying healthy to a ripe old age send us into denial about our own mortality? Let's hope not, because the contemplation of death can make our lives more meaningful and less stressful, as "Mortal Thoughts," by psychologist Michael W. Wiederman explains (*page 58*). Every day is a fresh chance to live a healthier, happier life.

Dawn Stover
Issue Editor
editors@sciam.com

© 2015 Scientific American

SCIENTIFIC AMERICAN

Volume 24, No. 1, Spring 2015

SPECIAL EDITION

Secrets of Staying Young

1 **Introduction: To Your Health!**

WHY WE AGE: EVOLUTION AT WORK

4 **Long Live the Humans**
Modern genomes and ancient mummies offer clues to why the life span of *Homo sapiens* far exceeds that of other primates. *By Heather Pringle*

12 **Why Can't We Live Forever?**
As we grow old, our cells begin to betray us. *By Thomas Kirkwood*

20 **The Myth of Antioxidants**
The idea that oxidative damage causes aging and that vitamins might preserve our youth is now in doubt. *By Melinda Wenner Moyer*

26 **Why Women Live Longer**
Stress alone does not explain the longevity gap. *By Thomas Kirkwood*

28 **The Evolution of Grandparents**
The rise of senior citizens may have played a big role in the success of our species. *By Rachel Caspari*

HOW TO STAY SMART AND STRONG

34 **Memory in Old Age: Not a Lost Cause**
Researchers have found ways to lessen age-related forgetfulness. *By Hal Arkowitz and Scott O. Lilienfeld*

36 **Slowing Age-Based Memory Loss**
To improve recall of words and faces, try associating them with locations. *By Shelly Fan*

38 **It's Not Dementia, It's Your Heart Medication**
Why cholesterol drugs might affect memory. *By Melinda Wenner Moyer*

40 **Fit Body, Fit Mind?**
Staying sharp into old age is not just a matter of winning the genetic lottery. *By Christopher Hertzog, Arthur F. Kramer, Robert S. Wilson and Ulman Lindenberger*

48 **Why Exercise Works Magic**
Being active is good for us for many reasons beyond the old familiar ones. *By Shari S. Bassuk, Timothy S. Church and JoAnn E. Manson*

54 **Killer Chairs**
Standing more could lower risk for obesity, illness and death, studies suggest. *By James Levine*

56 **Is Fasting Good for You?**
Intermittent fasting might improve health, at least according to research in animals. *By David Stipp*

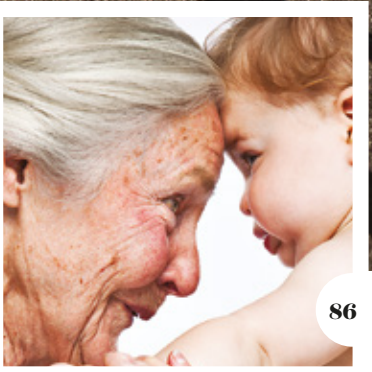
58 **Mortal Thoughts**
Thinking about death can ease our angst and make us better people, too. *By Michael W. Wiederman*

JORDAN SIEMENS Getty Images (runners)

© 2015 Scientific American

26

40


86

PROSPECTS FOR TREATMENT

66 Alzheimer's: Forestalling the Darkness
Intervening before symptoms appear could be key to combating the leading cause of dementia. *By Gary Stix*

74 Scanning for Alzheimer's
A new test can identify the disorder's early stages. How will it help patients? *By Ingfei Chen*

76 The Regenerating Brain
Stem cell therapy is emerging as a promising treatment for Parkinson's disease. *By Lydia Denworth*

84 Never Too Old for Chemo?
As the number of patients with cancer soars, researchers explore how best to treat them. *By Claudia Wallis*

CLUES TO SLOWING AGING

86 A New Path to Longevity
Scientists have uncovered an ancient mechanism that retards aging. Drugs that tweaked it could well postpone diseases of old age. *By David Stipp*

94 Seeds of Dementia
A chain reaction of toxic proteins may help explain Alzheimer's, Parkinson's and other killers—and could suggest new treatment options.
By Lary C. Walker and Mathias Jucker

100 The Oldest Old
People in their late 90s or older are often healthier and more robust than those 20 years younger. Traditional views of aging may need rethinking. *By Thomas T. Perls*

106 If Humans Were Built to Last
We would look a lot different if evolution had designed the human body to work well for a century or more.
By S. Jay Olshansky, Bruce A. Carnes and Robert N. Butler

112 Which Creatures Live the Longest?
The key indicator for animals may be total energy expended over a lifetime. *By Fred Guterl*

Articles in this special issue are updated from previous issues of *Scientific American* and *Scientific American Mind*.

Scientific American Special (ISSN 1936-1513), Volume 24, Number 1, Spring 2015, published by Scientific American, a division of Nature America, Inc., 75 Varick Street, 9th Floor, New York, NY 10013-1917. Canadian BN No. 127387652RT; TVQ1218059275 TQ0001. To purchase additional quantities: U.S., $13.95 each; elsewhere, $17.95 each. Send payment to Scientific American Back Issues, 75 Varick Street, 9th Floor, New York, NY 10013-1917. **Inquiries: fax 212-355-0408 or telephone 212-451-8415. Printed in U.S.A.**

Copyright © 2015 Scientific American, a division of Nature America, Inc. All rights reserved.

SECRETS OF STAYING YOUNG

© 2015 Scientific American

EVOLUTION

LONG LIVE THE HUMANS

Modern genomes and ancient mummies are yielding clues to why the life span of *Homo sapiens* far exceeds that of other primates

By Heather Pringle

© 2015 Scientific American

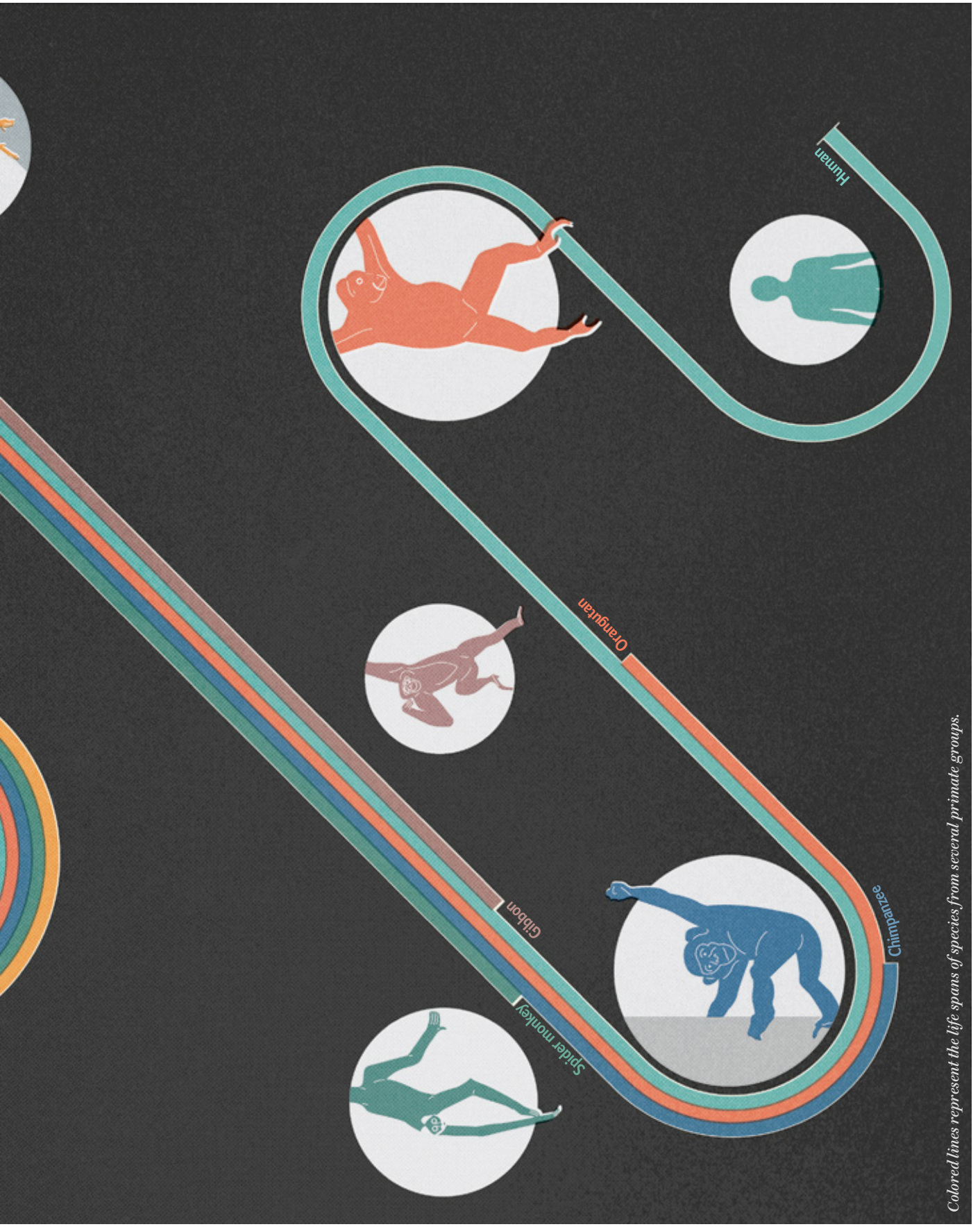


Illustration by Gavin Potenza

© 2015 Scientific American

ON A SUNDAY MORNING IN A DECAYING AND DANGEROUS INNER-CITY BARRIO IN Lima, Peru, an unmarked white van carrying nearly a dozen bodies rumbles to a stop on the grounds of the National Institute of Neurological Sciences. Seated in a small waiting area to the rear of the building, a throng of well-dressed researchers and government officials watches intently. As the driver clambers out, an assistant hustles off in search of a hospital gurney. Within minutes, two men wheel the first body into the institute's imaging unit.

Onlooker Caleb Finch, a biologist at the University of Southern California, has been waiting for this moment for months. Tall, gaunt and graying, with a Father Time–style beard, the 75-year-old scientist has devoted his career to the study of human aging. Our kind is remarkably long-lived compared with other primates. Our nearest surviving relatives, the chimpanzees, have a life expectancy at birth of about 13 years. In contrast, babies born in the U.S. in 2009 possessed a life expectancy at birth of 78.5 years. Finch has come to Lima to find out why—by peering into the distant past. The cadavers in the van belong to men, women and children who perished along this stretch of coastal desert as much as 1,800 years ago, long before the Spanish conquest. Cocooned in dusty textiles and interred in arid desert tombs, their naturally mummified bodies preserve critical new clues to the mystery of human longevity. As envoys from an era long before modern health care, they will offer case studies of aging in the past. Finch walks over to the van, grinning as he surveys the cargo. "That's a pack of mummies," he says.

Most researchers chalk up our supersized life span to the advent of vaccines, antibiotics and other medical advances, the development of efficient urban sanitation systems, and the availability of fresh, nutritious vegetables and fruit year-round. Indeed, much demographic evidence shows that these factors greatly extended human life over the past 200 years. But critical as they were to extending human life, they are only part of the longevity puzzle, Finch warrants. Marshaling data from fields as diverse as physical anthropology, primatology, genetics and medicine, he now proposes a controversial new hypothesis: that the trend toward slower aging and longer lives began much, much earlier, as our human ancestors evolved an increasingly powerful defense system to fight off the many pathogens and irritants in ancient environments. If Finch is right, future research on the complex links among infection, host defense and the chronic diseases of the elderly may revolutionize scientists' understanding of aging and how to cope with the challenges it brings.

AND MANY MORE

HINTS THAT MODERN HEALTH practices might not be solely responsible for our long life span have come from studies of contemporary hunter-gatherer groups. In 1985 Nicholas Blurton-Jones, a biological anthropologist at the University of California, Los Angeles, set off by Land Rover across the trackless bush in Tanzania's Lake Eyasi basin. With field assistant Gudo Mahiya, Blurton-Jones traveled to the isolated camps of the Hadza, hunter-gatherers who lived much as their ancestors had, hunting baboons and wildebeest, digging starchy tubers and collecting honey during the

IN BRIEF

Humans live far longer than other primates, a phenomenon that has traditionally been credited to modern medicine, food availability and sanitation systems.

But new research suggests that although these factors have extended human life span over the past 200 years, the trend actually began far earlier than that.

As human ancestors ate more meat, they evolved defenses against its attendant pathogens. These defenses contribute to longevity but foster disease later in life.

© 2015 Scientific American

Medical imaging of ancient mummies such as Egyptian scribe Hatiay has revealed clogged arteries, suggesting that cardiovascular disease is not a modern affliction but rather the price humans pay for having a supercharged immune system.

MICHAEL MIYAMOTO *AP Photo (mummy)*; COURTESY OF M. LINDA SUTHERLAND *(CT scan)*

rainy season from hives of the African honeybee. Journeying from one camp to another, the two researchers collected basic demographic data, checking each Hadza household and recording the names and ages of the inhabitants. Then the pair updated this census information six times in the 15 years that followed, noting down the names of all who had died and the causes of their death. In addition, Blurton-Jones obtained some earlier census data on the Hadza from two other researchers.

The Hadza lived—as ancient humans and chimpanzees did—in a natural environment teeming with pathogens and parasites. They lacked running water and sewage systems, defecating in a zone 20 to 40 meters away from their camps, and they rarely sought out medical care. Yet as Blurton-Jones and Mahiya discovered, the Hadza enjoyed much longer lives than chimpanzees did. Indeed, the Hadza had a life expectancy at birth of 32.7 years. And if they reached adulthood, they could expect to live 40 more years, nearly three times longer than a chimpanzee reaching adulthood. Some Hadza elders survived into their 80s. Clearly, their relatively long lives owed little to medical and technological advances.

Moreover, the Hadza were not alone. In 2007 two anthropologists, Michael Gurven of U.C. Santa Barbara and Hillard Kaplan of the University of New Mexico analyzed data from all five modern hunter-gatherer societies that researchers had studied

© 2015 Scientific American

demographically. Infections counted for 72 percent of the deaths, and each group revealed a very similar J-shaped mortality curve—with child mortality as high as 30 percent, low death rates in early adulthood and exponentially rising mortality after the age of 40. Then Gurven and Kaplan compared these curves with those of both wild and captive chimpanzees: the simians experienced the sharp uptick of adult mortality at least 10 years earlier than human hunter-gatherers. "It appears that chimpanzees age much faster than humans," concluded Gurven and Kaplan in their paper detailing the findings, "and die earlier, even in protected environments."

Yet when, exactly, did humans begin living longer? To obtain clues, anthropologists Rachel Caspari of Central Michigan University and Sang-Hee Lee of U.C. Riverside examined the remains of 768 individuals from four ancestral human groups spanning millions of years. By assessing the degree of dental wear, which accumulates at a constant pace from chewing, they estimated the ratio of young adults around 15 years of age to older adults around age 30 (old enough to be a grandparent) in each of the four groups. Their studies revealed that living to 30 and beyond became common only recently in our prehistoric past. Among the australopithecines, which emerged in Africa around 4.4 million years ago, most individuals died before their 30th birthday. Moreover, the ratio of thirtysomethings to 15-year-olds was just 0.12. In contrast, *Homo sapiens* who roamed Europe between 44,000 and 10,000 years ago often lived to 30 or more, achieving a ratio of 2.08 [see "The Evolution of Grandparents," by Rachel Caspari, on page 28].

Calculating the life expectancy of early *H. sapiens* populations is challenging, however: detailed demographic data, such as those supplied by both census records and death registrations, are lacking for much of our long past. So Finch and his colleague Eileen Crimmins, a gerontologist at the University of Southern California, analyzed the earliest, virtually complete statistical set of that nature available—data first gathered in Sweden in 1751, decades before the advent of modern medicine and hygiene. The study revealed that mid-18th-century Swedes had a life expectancy at birth of 35. But those who survived bacterial infections and contagious diseases such as smallpox during childhood and reached the age of 20 could reasonably look forward to another 40 years.

To Finch, these findings raised a major question. The 18th-century Swedes lived cheek by jowl in large, permanent villages, towns and cities, where they were exposed to serious health risks unknown to small communities of mobile chimpanzees. So why did the Swedes live longer? The answer, it turns out, may lie in the meaty diets of their early human ancestors and the evolution of genes that protected them from the many hazards of carnivory.

MEAT-EATING GENES

CHIMPANZEES SPEND most of their waking hours in a sweet pursuit: foraging for figs and other ripe fruits. In search of fructose-rich fare, they range over large territories, only occasionally using the same night nest twice in a row. They are skilled at hunting small mammals such as the red colobus monkey, but they do not deliberately set out searching for these prey. Nor do they consume large quantities of meat. Primatologists studying wild chimpanzees in Tanzania have calculated that meat makes up 5 percent or less of the simians' annual diet there, whereas research in Uganda shows that animal fat constitutes only 2.5 percent of their yearly fare by dry weight.

In all likelihood, Finch says, the earliest members of the human family consumed a similar plant-based diet. Yet sometime between 3.4 million and 2.5 million years ago, our ancestors incorporated a major new source of animal protein. As sites in Ethiopia show, they began butchering the remains of large, hoofed mammals such as antelopes with simple stone tools, smashing the bones to get at the fat-rich marrow, slicing off strips of meat, and leaving behind telltale cut marks on femurs and ribs. And by 1.8 million years ago, if not earlier, humans began actively hunting large game and bringing entire carcasses back to camp. The new abundance of calories and protein most likely helped to fuel brain growth but also increased exposure to infections. Finch suggests that this risk favored the rise and spread of adaptations that allowed our predecessors to survive attacks by pathogens and thus live longer.

The trend toward increasing carnivory would have exposed our ancestors to pathogens in several ways. Early humans who scavenged the carcasses of dead animals, and who dined on raw meat and viscera, boosted their chances of ingesting infectious pathogens. Moreover, as humans took up hunting large animals, they faced greater risks of lacerations and fractured bones when closing in on their prey: such injuries could lead to deadly infections. Even cookery, which may have emerged as early as one million years ago, if not earlier, posed perils. Inhaling wood smoke daily exposes humans to high levels of endotoxins and soot particles. Roasting and charring meat improves both the taste and digestibility but creates chemical modifications known as advanced glycation end products, which contribute to serious diseases such as diabetes. Our ancestors' later embrace of agriculture and animal husbandry, which began some 11,500 years ago, added new dangers. The daily proximity of humans to domesticated goats, sheep, pigs, cattle and chickens, for example, elevated the risk of contracting bacterial and viral infections from animals. Moreover, as families settled permanently in villages, sewage from humans and livestock contaminated local water supplies. Pathogenic bacteria thrived.

Even so, humans exposed to such health risks in 1751 in Sweden lived longer than their simian relatives. To tease out clues to this longevity, Finch began studying the scientific literature on chimpanzee and human genomes. Previously published studies by others showed that the two genomes were around 99 percent identical. But in the uniquely human 1 percent, evolutionary biologist Hernán Dopazo, then at the Prince Felipe Research Center in Valencia, Spain, and his colleagues discerned a disproportionately high number of genes that had undergone positive selection and that played key roles in host defense and immunity—specifically in a part of the defense system known as the inflammatory response. Positive selection favors genes that hone our ability to survive and reproduce, which allows them to become more frequent in populations over time, a process that leaves a distinctive "signature" in the DNA sequence. Dopazo's findings added new weight to an idea growing in Finch's mind. He wondered if natural selection had endowed ancient humans with a souped-up system for fighting off the microbial threats and warding off other health hazards posed by increased meat consumption, thereby extending our life span.

In the war against bacteria, viruses and other microbes that

© 2015 Scientific American

seek to invade our tissues, the human host defense system brandishes two powerful weapons: the innate immune system and the adaptive immune system. The innate system is the first responder. It mobilizes immediately at the scene of an attack or injury to eliminate pathogens and heal damaged tissue, and it essentially responds in the same way to all threats. The adaptive system, in contrast, kicks into gear more slowly, customizing its response to particular pathogens. In doing so, it creates an immunological memory that confers lifelong protection against the invader.

The inflammatory response is part of the innate immune system. It goes to work when tissues suffer damage from microbes, traumatic wounds, injuries or toxins, and, as Finch points out, physicians have long recognized its hallmarks. Some 2,000 years ago Aulus Cornelius Celsus, a Roman medical author, described four cardinal signs of inflammation—heat, redness, swelling and pain. The heat and redness come from a swift and marked increase in the flow of warm blood to the damaged tissue. Swelling then results from increased vascular permeability, which causes blood cells and plasma to leak into the affected area, carrying proteins that can assist in preventing the spread of infection and in initiating wound healing.

Finch began examining the human-specific changes in genes related to host defense. He was quickly struck by the changes that had affected the *apolipoprotein E* (*APOE*) gene. This important gene strongly influences the transport and metabolism of lipids, the development of the brain and the workings of the immune system. It has three primary, uniquely human variants (alleles), of which *APOE* e4 and *APOE* e3 are the most prevalent.

APOE e4's DNA sequences closely resemble those in chimpanzee *APOE,* strongly suggesting that it is the ancestral human variant that emerged near the beginning of the *Homo* genus more than two million years ago and thus may have had the earliest effect on our longevity. Differing in several critical amino acids from the chimp version, *APOE* e4 vigorously ramps up the acute phase of inflammation. It boosts the production of proteins such as interleukin-6, which helps to increase body temperature, and tumor necrosis factor–alpha, which induces fever and inhibits viruses from replicating. Equipped with this supercharged defense system, children in ancient human families had a better chance of fighting off harmful microbes that they unwittingly ingested in food and encountered in their surroundings. "When humans left the canopy and went out onto the savanna," Finch notes, "they had a much higher exposure to infectious stimuli. The savanna is knee-deep in herbivore dung, and humans were out there in bare feet."

Moreover, early humans who carried *APOE* e4 most likely profited in another key way. This variant facilitates both the intestinal absorption of lipids and the efficient storage of fat in body tissue. During times when game was scarce and hunting poor, early *APOE* e4 carriers could draw on this banked fat, upping the odds of their survival.

Even today children who carry *APOE* e4 enjoy an advantage over those who do not. In one study of youngsters from impoverished families living in a Brazilian shantytown, *APOE* e4 carriers succumbed to fewer bouts of diarrheal disease brought on by *Escherichia coli* or *Giardia* infections than noncarriers did. And they scored higher on cognitive tests, most likely as a result of their greater absorption of cholesterol—a dietary requirement for neurons to develop in the brain. "So this would have been adaptive, we think," Finch remarks.

A DEFERRED COST

ALL TOLD, *APOE* e4 seems to be a key part of the puzzle of human longevity. Ironically, now that we live longer, this gene variant appears to double-cross us later in life. Its debilitating effects became apparent only as our human ancestors increasingly survived to middle age and beyond. In Lima, Finch and an international team of cardiologists, radiologists, biologists and anthropologists are searching for traces of these afflictions in the preserved cardiovascular tissues of ancient adult mummies.

EIGHTEENTH-CENTURY SWEDES LIVED CHEEK BY JOWL IN LARGE, PERMANENT VILLAGES, TOWNS AND CITIES, WHERE THEY WERE EXPOSED TO SERIOUS HEALTH RISKS UNKNOWN TO SMALL COMMUNITIES OF MOBILE CHIMPANZEES. SO WHY DID THE SWEDES LIVE LONGER?

Inside the crowded imaging unit in Lima, Finch hovers over a technician's computer. It has been a long, trying morning. Several of the mummy bundles transported to the unit are too large to fit into the CT scanner. Others, when scanned, reveal little more than skeletal remains, raising doubts that the preservation of human tissue in the bundles will be adequate for the study.

But no one is giving up. On the screen is a crisp, three-dimensional CT scan of a bundle just wheeled in from the van. Hunching forward, cardiologists Gregory Thomas of Long Beach Memorial Medical Center in California and Randall C. Thompson of the University of Missouri School of Medicine–Kansas City scrutinize an anatomical landscape rendered strangely foreign by centuries of decay and desiccation. As the technician scrolls up and down the image, the two cardiologists gradually pick out preserved soft tissue and the snaking trails of major arteries. The relief in the room is palpable. Then, unable to resist, the two cardiologists take a quick preliminary look along the arteries for small, dense, white patches—calcified plaque that signals an advanced stage of atherosclerosis, or hardening of the arteries, the leading cause of fatal heart attacks and strokes. The individual has clearly calcified arteries.

Cardiologists have traditionally regarded atherosclerosis as a disease of modern civilization. Contemporary behaviors such as smoking cigarettes, eschewing exercise, dining on high-calorie diets and packing on the pounds are all known to increase the risk of this disease. Moreover, several recent studies point to an emerging atherosclerosis epidemic in the developing world, as societies there grow more affluent and increasingly embrace a modern, Western lifestyle. Yet in 2010 Thomas and a group of his colleagues decided to test the idea that atherosclerosis is a disease of modern, affluent life by taking CT scans of ancient human mummies and examining their arteries.

© 2015 Scientific American

NAFTALI HILGER *Redux Pictures*

Modern hunter-gatherers such as the Hadza of Tanzania live in natural environments filled with parasites and pathogens, just as chimpanzees do. Yet they live far longer than chimps—perhaps because of genes that adapted humans to eating meat.

The team started in Egypt, with 52 mummies dating between 3,500 and 2,000 years ago. Biological anthropologist Muhammad Al-Tohamy Soliman of the National Research Center in Giza estimated the age at death for each individual, based on an examination of dental and skeletal development. Then the medical team pored over the scans. Discussing the images during weekly Skype calls, they identified cardiovascular tissue in nearly 85 percent of the mummies. To their surprise, 45 percent of these had definite or probable atherosclerosis—clear evidence that one ancient population suffered from the disease. "We were [also] a bit surprised by just how much atherosclerosis we found in ancient Egyptians who were young," recalls team member James Sutherland, a radiologist at the South Coast Radiological Medical Group in Laguna Hills, Calif. "The average age of death was around 40."

When their paper came out in the *Journal of the American College of Cardiology* in the spring of 2011, Finch contacted the team immediately, proposing a new explanation for the high levels of atherosclerosis detected in the study. The ancient Egyptians, Finch noted, were no strangers to pestilence and infection. Previous studies showed that many ancient Egyptians were exposed to a wide range of infectious diseases, including malaria, tuberculosis and schistosomiasis (an ailment caused by tiny parasitic worms found in contaminated water). *APOE* e4 carriers, with their enhanced immune systems, tended to survive many childhood infections. But they experienced decades' worth of chronic high levels of inflammation in the pathogen-rich environment—levels that are now linked to several deadly diseases of old age, including atherosclerosis and Alzheimer's. Indeed, the arterial plaques that characterize atherosclerosis seem to accumulate during inflammation and wound healing in the vascular wall. "And while it might be pushing it to say the senile plaques of Alzheimer's are some form of scab, like the plaques on artery vessels, they have many of the same components," Finch suggests.

Thomas and his colleagues asked Finch to join their team. Together they decided to gather more data, examining the cardiovascular tissues of ancient mummies from a wide range of cultures. The Egyptians in their first study likely came from affluent upper classes that could afford mummification: such individuals may have exercised rarely and dined frequently on high-calorie foods. So the team expanded the study to other, very different cultures. They examined existing CT scans of ancestral Puebloan mummies from Utah and century-old Unan-

© 2015 Scientific American

gan mummies from Alaska. In addition, they analyzed the scans they had taken of pre-Hispanic mummies from coastal Peru. Those individuals dated to as early as 1500 B.C.

In March 2013 the team published its findings in the *Lancet*. Among the 137 examined mummies, 34 percent had probable or definite atherosclerosis. Significantly, the scans revealed the disease in all four ancient populations, including the hunting-and-gathering Unangan people, who ate a largely marine diet. The findings clearly challenged the idea that atherosclerosis was a modern disease and pointed to another explanation. "The high level of chronic infection and inflammation in premodern conditions might have promoted the inflammatory aspects of atherosclerosis," the team wrote.

THE FINDINGS CLEARLY CHALLENGED THE IDEA THAT ATHEROSCLEROSIS WAS A MODERN DISEASE AND POINTED TO ANOTHER EXPLANATION.

Perhaps, Finch says, the ancient gene variant that ramped up our inflammatory response and boosted the chances of our survival to the age of reproduction—*APOE* e4—came with a steep, deferred cost: heart attacks, strokes, and other chronic diseases of aging. In fact, *APOE* e4 appears to be a classic case of something biologists call antagonistic pleiotropy, in which a gene has a strong positive effect on the young and an adverse impact on the old. "I think these are very intriguing ideas," says Steven N. Austad, a biologist and gerontologist at the University of Alabama at Birmingham. "And what evidence we have supports them."

REFINING IMMUNE RESPONSE

RESEARCH ALSO POINTS TO other gene variants that contributed to our longevity. At roughly the same time that *H. sapiens* emerged in Africa some 200,000 years ago, a second major *APOE* variant emerged. This allele, known as *APOE* e3, enhanced health among adults in the 40- to 70-year-old range and helped to slow the aging process, and today it has a prevalence of between 60 and 90 percent in human populations. As Finch points out, *APOE* e3 carriers produce a less vigorous inflammatory response than those with the ancestral variant. Moreover, they appear better adapted to meat- and fat-rich diets. Generally speaking, they have lower blood cholesterol and are less prone to the diseases that strip the old of their vitality: coronary heart disease, cognitive decline and Alzheimer's. Indeed, carriers of the more recent variant enjoy life expectancies as much as six years longer than their *APOE* e4 neighbors. "*APOE* e3," Finch notes, "may have been a factor in the evolution of long life spans."

APOE is not the only gene linked to the evolution of human longevity, however. At U.C. San Diego, Ajit Varki, a professor of medicine, and his colleagues are investigating several other genes that may have undergone changes that boosted our chances of survival and extended our lives. Varki's research focuses on the *SIGLEC* genes that play key roles related to host defense. These genes express proteins that straddle our cell membranes and act a little like sentries. Their function "is to recognize friends, not foes," Varki explains. It is no easy matter. To fool these sentries, infectious pathogens evolve camouflage consisting of proteins that mimic those borne by "friends."

In 2012 Varki and his team published a study in the *Proceedings of the National Academy of Sciences USA* that identified two key changes in these genes that dated to at least 200,000 to 100,000 years ago and that honed our ability to fight off pathogens. One change produced a new human variant of the ancestral primate gene *SIGLEC 17*. This variant, however, was nonfunctional. A second event deleted the ancestral gene *SIGLEC 13* entirely. To better understand these changes, Varki and his colleagues experimentally resurrected the proteins once expressed by *SIGLEC 13* and *17*. Both ancestral proteins, they discovered, had been "hacked" by pathogens responsible for two life-threatening infections in babies: group B *Streptococcus* and *E. coli* K1. So as natural selection began weeding out these compromised genes from our genome, the odds of survival rose in human infants.

Such findings add new fuel to the hypothesis that pumped-up immune systems played a key role in lengthening human lives. "Our immune systems went through a lot of changes," Varki says. And as geneticists and biologists continue to investigate the uniquely human part of our genome, many are starting to look for other genetic variants and events that contributed to our long lives today.

Yet already the findings are giving some researchers pause for thought. Public health messages have long warned that lifestyle choices such as couch-potato evenings and calorie-rich diets are largely to blame for the high incidence of atherosclerosis, heart attacks and strokes. But the new research—particularly the studies on ancient mummies—suggests that the picture may not be quite so simple. Our DNA and an overcharged immune system may well contribute to the development of such diseases. "So maybe we have a little less control over atherosclerosis than we thought," muses cardiologist Thompson. "Maybe our mental framework should be shifted." And perhaps, he adds, researchers should be looking for undiscovered risk factors.

The new findings are also raising a fundamental question about human longevity. Can we, or should we, expect the trend toward longer lives to continue? Some scientists have predicted that babies born after 2000 in countries where life expectancy had already been high—including the U.S., Canada, the U.K. and Japan—will live to 100 years of age. Finch is quietly skeptical, however. The emerging trend toward obesity in many human populations and toward environmental deterioration brought about by climate change, he says, could well affect human longevity negatively and throw a major wrench into the works. "I think there is a reason to be cautious about that," Finch concludes. "But time will tell." SA

Heather Pringle is a Canadian science writer and a contributing correspondent for *Science*.

MORE TO EXPLORE

Evolution of the Human Lifespan and Diseases of Aging: Roles of Infection, Inflammation, and Nutrition. Caleb E. Finch in *Proceedings of the National Academy of Sciences USA*, Vol. 107, Supplement No. 1, pages 1718–1724; January 26, 2010.

Atherosclerosis across 4000 Years of Human History: The Horus Study of Four Ancient Populations. Randall C. Thompson et al. in *Lancet*, Vol. 381, pages 1211–1222; April 2013.

Computed Tomographic Evidence of Atherosclerosis in the Mummified Remains of Humans from around the World. Randall C. Thompson et al. in *Global Heart*, Vol. 9, No. 2, pages 187–196; June 2014.

© 2015 Scientific American

MEDICINE

WHY CAN'T WE LIVE FOREVER?

As we grow old, our own cells begin to betray us. By unraveling the mysteries of aging, scientists may be able to make our lives longer and healthier

By Thomas Kirkwood

IF YOU WERE GIVEN A FREE HAND TO PLAN HOW YOUR LIFE WILL END—YOUR LAST WEEKS, DAYS, hours and minutes—what would you choose? Would you, for example, want to remain in great shape right up until the last minute and then go quickly? Many people say they would choose that option, but I see an important catch. If you are feeling fine one moment, the very last thing you would want is to drop dead the next. And for your loving family and friends, who would suffer instant bereavement, your sudden death would be a cruel loss. On the other hand, coping with a long, drawn-out terminal illness is not great either, nor is the nightmare of losing a loved one into the dark wastes of dementia.

IN BRIEF

The average life span of humans continues to lengthen, and some scientists have begun to ponder whether this trend will continue indefinitely.

Not every species ages, and some research suggests that drugs or changes in diet may slow metabolism or alter basic aging processes so that we can live longer.

All proposed longevity strategies remain unproved, however, and strategies that maintain and repair cells may impair growth and reproduction.

JON KRAUSE

© 2015 Scientific American

© 2015 Scientific American

We all prefer to avoid thinking about the end of life. Yet it is healthy to ask such questions, at least sometimes, for ourselves and to correctly define the goals of medical policy and research. It is also important to ask just how far science can help in efforts to cheat death.

WE'RE LIVING LONGER

IT IS OFTEN SAID that our ancestors had an easier relationship with death, if only because they saw it so much more often. Just 100 years ago life expectancy was shorter by around 25 years in the West. This literal fact of life resulted because so many children and young adults perished prematurely from a whole variety of causes. A quarter of children died of infection before their fifth birthday; young women frequently succumbed to complications of childbirth; and even a young gardener, scratching his hand on a thorn, might be lost to fatal blood poisoning.

Over the course of the past century sanitation and medical care so dramatically reduced death rates in the early and middle years of life that most people now pass away much later, and the population as a whole is older than ever before. Life expectancy is still increasing worldwide. In the richer countries around the world it lengthens five hours or more every day, and in many developing countries that are catching up the rate quickens still faster. Today the dominant cause of death is the aging process itself and the various diseases to which it gives rise—whether cancer, which drives cells to proliferate out of control, or Alzheimer's disease, at the opposite pole, which causes premature death of brain cells.

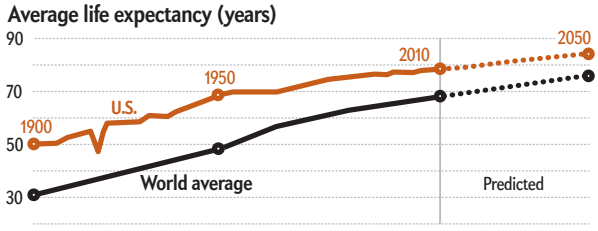
Until as recently as 1990, demographers predicted confidently that the historical trend of increasing life expectancy would soon cease. Aging, many researchers believed, was fixed—a process programmed into our biology that resulted in a built-in time of death.

No one foresaw the continued increase in life expectancy. It has taken politicians and planners by surprise. Scientists are still coming to terms with the notion that aging is not fixed, that average life spans have not reached a limit. They change and continue to change, stretched for reasons that researchers do not fully understand. The declining death rates of the very old are now driving human life expectancy into uncharted territory. If the prevail-

LONGEVITY METER

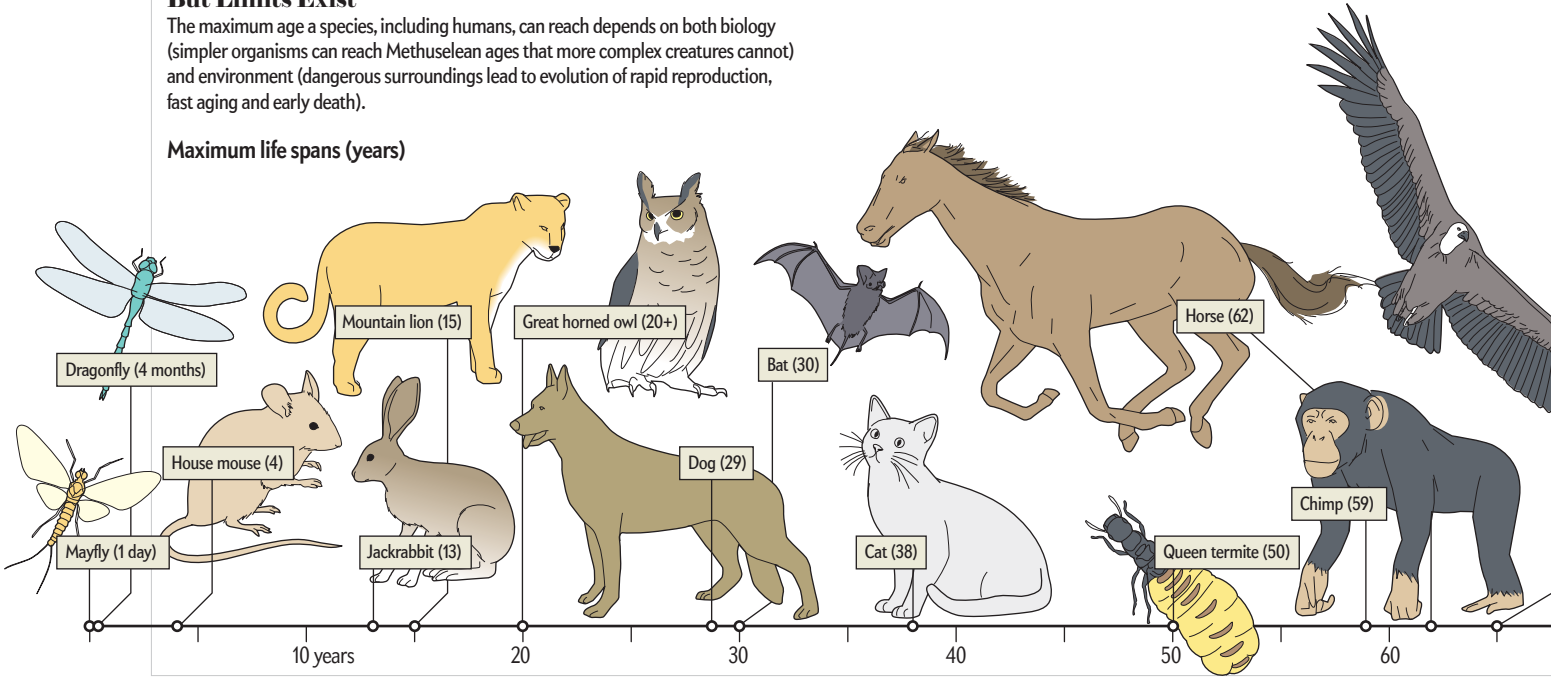
How Much More Can Life Span Increase?

Human life expectancy, or average life span, has been rising for more than 100 years in the U.S. and globally (*graph*). Evidence suggests, however, that biological constraints keep most species from surpassing age limits specific to that species (*below*). Investigators hope interventions aimed at relaxing such constraints will extend today's maximum achievable life span or will at least help people stay healthy longer than they do now.



Lives Get Longer
Advances in medicine and sanitation have extended human life spans in the U.S. and around the world.

But Limits Exist
The maximum age a species, including humans, can reach depends on both biology (simpler organisms can reach Methuselean ages that more complex creatures cannot) and environment (dangerous surroundings lead to evolution of rapid reproduction, fast aging and early death).



© 2015 Scientific American

ing certainties about human aging have crumbled, what then is left? What does science actually know about the aging process?

Accepting new ideas is not always easy, because scientists are humans, too, and we have all grown up with fairly rigid preconceptions about how the body ages. Some years ago, while I was driving with my family in Africa, a goat ran under the wheels of our vehicle and was killed instantly. When I explained to my six-year-old daughter what just happened, she asked, "Was it a young goat or an old goat?" I was curious why she wanted to know. "If it was old, it's not as sad, because it wouldn't have had so long to live anyway," came her answer. I was impressed. If such sophisticated attitudes to death form this early, small wonder that modern science struggles to come to terms with the reality that most of what we thought we knew about aging is wrong.

To explore current thinking about what controls aging, let us begin by imagining a body at the very end of life. The last breath is taken, death takes hold and life is over. At this moment, most of the body's cells are still alive. Unaware of what just happened, they carry out, to the best of their abilities, the metabolic functions that support life—procuring oxygen and nutrients from the surrounding environment and using them to generate the energy needed to make and power the activities of proteins (the main working parts of cells) and other cellular components.

In a short while, starved of oxygen, the cells will die. With their death, something of immense antiquity will come to its own quiet end. Each and every one of the cells in the body that just died could, if the records were available, trace its ancestry through an unbroken chain of cell divisions backward in time through an almost unimaginable four billion years to the emergence of the earliest forms of cellular life on this planet.

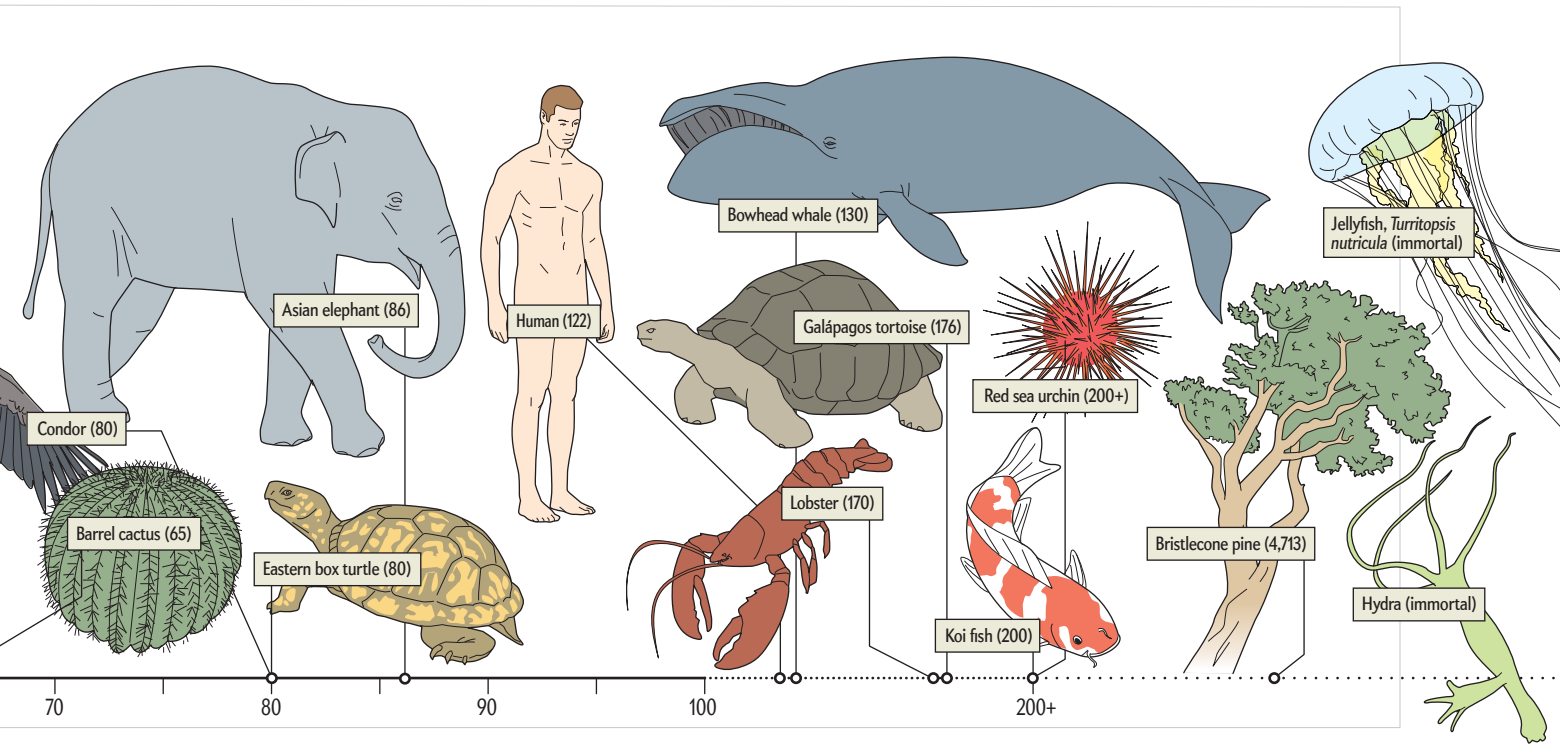
Death is assured. But some of your cells, at least, have this astonishing property: they are endowed with something as near to immortality as can be attained on earth. When your death occurs, only a tiny number of your cells will continue this immortal lineage into the future—and then only if you have children. Only one cell of your body escapes extinction—a sperm or an egg—for each surviving child. Babies are born, grow, mature and reproduce, and so it continues.

The scenario we have just imagined reveals not only the fate of our mortal body, or "soma," made up of all the nonreproductive cells, but also the almost miraculous immortality of the cellular lineage to which we belong. The central puzzle in aging science, from which all else follows, is, Why do most creatures have a mortal soma? Why is it that evolution has not led all our cells to enjoy the apparent immortality of the reproductive lineage, or germ line, as represented by the sperm and the egg? This puzzle was first recognized by 19th-century German naturalist August Weismann, and a solution occurred to me in the bath one winter night in early 1977. I believe that the answer, now called the disposable soma theory, goes a long way toward explaining why different species age as they do.

WHY WE AGE AS WE DO

THE THEORY is best understood by considering the challenges cells and complex organisms face as they try to survive. Cells are damaged all the time—DNA gets mutated, proteins get damaged, highly reactive molecules called free radicals disrupt membranes, and the list goes on. Life depends on the continual copying and translation of genetic data, and we know that the molecular machinery handling all these things, excellent as it may be, is not perfect. Considering all these challenges, the immortality of the germ line is actually remarkable.

Living cells operate constantly under threat of disruption, and the germ line is not immune. The reason that the germ line does not die out in a catastrophe of errors has to do, on the one hand,



JASON LEE (*animals*); LUCY READING-IKKANDA, SOURCE: "THE WORLD ECONOMY IN MILLENNIAL PERSPECTIVE," BY ANGUS MADDISON, OECD, 2001 (*world, 1900–1950*); "WORLD POPULATION AGEING, 2009," BY THE UNITED NATIONS, DECEMBER 2009 (*world, 1950–2050*); WWW.GAPMINDER.ORG (*U.S., 1800–2010*); U.S. CENSUS BUREAU, INTERNATIONAL DATA BASE AND CENTERS FOR DISEASE CONTROL AND PREVENTION (*U.S., 1950–2050*) (*graph*)

© 2015 Scientific American

with its highly sophisticated mechanisms for cellular self-maintenance and repair and, on the other hand, with its ability to get rid of its more serious mistakes through continual rounds of competition. Sperm are produced in vast excess; usually only a good one can fertilize the egg. Egg-forming cells are produced in much greater numbers than can ovulate; stringent quality control eliminates the ones that fail to make the grade. And finally, if errors slip past all these checks, natural selection provides the final arbiter of which individuals are the fittest to transmit their germ line to future generations.

After the seemingly miraculous feat of growing a complex body from a single cell—the fertilized egg—it should be relatively straightforward merely to keep a body going indefinitely—as American evolutionist George Williams has pointed out. Indeed, for some multicelled organisms, an absence of aging appears to be the rule. The freshwater hydra, for example, shows an extraordinary power of survival. Not only does the hydra apparently not age, in the sense that as it gets older it shows no increase in death rate or decline in fertility, it also appears capable of regrowing a whole new body from even a tiny fragment, if by chance it is cut into pieces. The secret of the hydra's eternal youth: quite simply, germ cells permeate its body. If the immortal germ line is everywhere, it actually comes as no surprise that an individual hydra can survive without any foreseeable end, presuming it does not succumb to injury or predators.

In most multicelled animals, however, the germ line is found only in the tissue of the gonads, where the sperm and eggs form. This arrangement provides great advantages. During the long history of evolution, it freed other cell types to become specialists—nerve, muscle and liver cells, among others, that are required for the development of any complex organism, whether a *Triceratops* or a human.

This division of labor had far-reaching consequences for how organisms age and how long they can live. As soon as the specialist cells surrendered the role of continuing the species, they also abandoned any need for immortality; they could die after the body had passed on its genetic legacy through the germ line to the next generation.

ULTIMATE TRADE-OFFS

SO HOW LONG can those specialist cells survive? In other words, how long can we and other complex organisms live? The answer for any given species has a lot to do with the environmental threats its ancestors faced as they evolved and with the energy costs of maintaining the body in good operating order.

By far the majority of natural organisms die at relatively young ages because of accidents, predation, infection or starvation. Wild mice, for example, are at the mercy of a very dangerous environment. They are killed rather quickly—it is rare for a wild mouse to see its first birthday. Bats, on the other hand, are safer because they can fly.

Meanwhile maintenance of the body is expensive, and resources are usually limited. Out of the daily intake of energy, some might go to growth, some to physical work and movement, some to reproduction. Some energy, instead, might be stored as fat to protect against famine, but much gets burned just to fix the innumerable faults that arise every second the organism is alive. Another increment of these scarce resources goes to proofread the genetic code involved in the continual synthesis of new proteins and other essential molecules. And still another allocation powers the energy-hungry garbage disposal mechanisms that clear molecular debris out of the way.

Here is where the disposable soma theory comes in. The theory posits that, like the human manufacturer of an everyday product—a car or a coat, for example—evolving species have to make trade-offs. It does not pay to invest in allowing indefinite survival if the environment is likely to bring death within a fairly predictable time frame. For the species to survive, a genome basically needs to keep an organism in good shape and enable it to reproduce successfully within that time span.

At all stages of life, even to its very end, the body does its utmost to stay alive—in other words, it is programmed not for aging and death but for survival. But under the intense pressure of natural selection, species end up placing higher priority on investing in growth and reproduction—in the perpetuation of the species—than on building a body that might last forever. So aging is driven by the gradual lifelong accumulation of diverse forms of unrepaired molecular and cellular damage.

No biological software program, then, dictates precisely when it is time to die, but growing evidence suggests that certain genes can nonetheless influence how long we live. Tom Johnson and Michael Klass, working with tiny nematode worms, discovered a gene with such an effect on longevity in the 1980s. Mutation of a gene that the researchers aptly named *age-1* produced a 40 percent increase in average life span. Since then, investigators in many laboratories have found numerous other genes capable of increasing nematode life span, and similar mutations have turned up in other animals, from fruit flies to mice.

The genes that extend life span mostly alter an organism's metabolism, the way it uses energy for bodily functions. Often investigators find these genes play a role in the insulin-signaling pathway, pivotal in metabolic regulation. The cascades of molecular interactions constituting this pathway shift the overall level of activity of literally hundreds of other genes responsible for controlling all the intricate processes that carry out cellular maintenance and repair. In effect, it seems that lengthening life span requires changing exactly those processes we know protect the body against buildup of damage.

The amount of food available also ratchets metabolism up or down. As long ago as the 1930s, researchers discovered, rather surprisingly, that underfeeding lab rodents extends their lives. Once again, modulating metabolism seems to have an effect on the rate of damage accumulation because mice subjected to dietary restriction increase the activity of a range of maintenance and repair systems. At first glance, it might seem strange that an animal short of food should spend more, not less, energy on bodily maintenance. A period of famine is, however, a bad time to reproduce, and some evidence suggests that during famines certain animals will do better to switch off their fertility, thereby diverting a large fraction of their remaining energy budget to cell maintenance.

OF MICE AND MEN

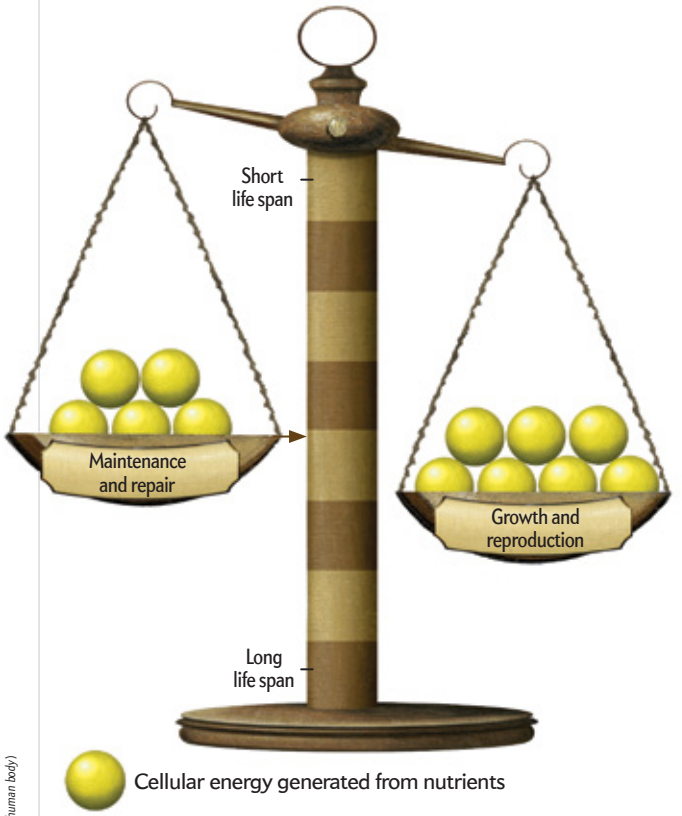
THIS NOTION of caloric restriction—and its purported ability to extend longevity—has captured the attention of people who wish to live longer. Humans who go hungry in the hope of a longer life should take note, though, that such a mechanism is much less likely to work for members of our species be-

© 2015 Scientific American

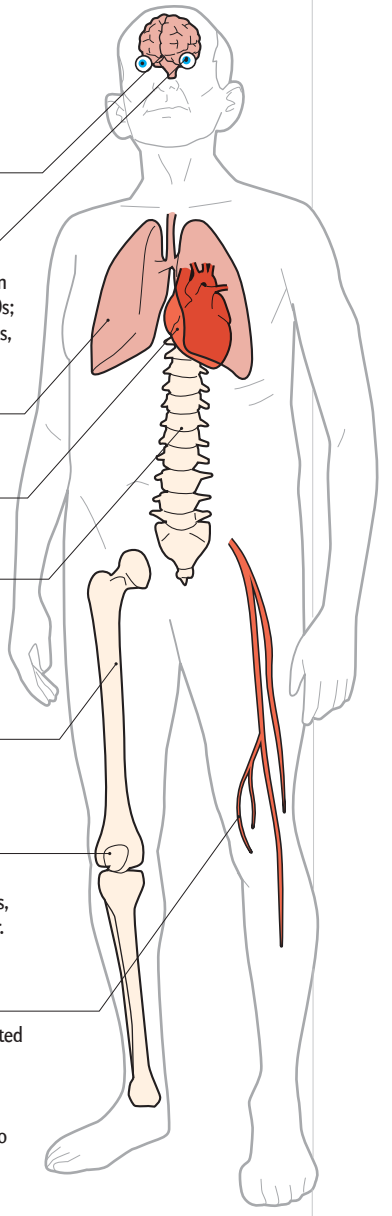
How Aging Stems from Trade-offs

Aging occurs because our body must make a trade-off between reproducing and staying in good repair, according to the author's "disposable soma" theory. Given a limited supply of energy, the amount that goes to making and protecting sperm and eggs tips the scale away from ensuring that "somatic" cells—skin, bone, muscle, and so on—remain in good condition. As a result, cells accumulate damage over time, which ultimately causes some organ or another to become diseased. If bodily functioning is sufficiently compromised, death ensues.

How Energy Is Allocated in the Body



Flagging Cell Repair Leads to a Gradual Decline



BRAIN
Memory and reaction time may begin to decline around age 70.

EYES
Difficulty focusing on close objects begins in 40s; ability to see fine detail decreases in 70s; from age 50, susceptibility to glare increases, and ability to see in dim light and to detect moving targets decreases.

LUNGS
Maximum breathing capacity diminishes by 40 percent between ages 20 and 80.

HEART
Heart rate during maximal exercise falls by 25 percent between ages 20 and 75.

SPINAL DISKS
Years of pressure on the spongy disks that separate the vertebrae can cause them to slip, rupture or bulge; then they, or the vertebrae themselves, can press painfully on nerves.

BONES
Bone mineral loss begins to outstrip replacement around age 35; loss speeds up in women at menopause.

JOINTS
Repetitive motions through the years thin the slippery protective coverings over joints, causing bones to grind against one another. The resulting pain may be exacerbated by osteoarthritis and other disorders.

VEINS
Veins in the legs become enlarged and twisted when small valves that should snap shut between heartbeats (to keep blood moving up toward the heart) malfunction, causing blood to pool. Severe varicosities can lead to swelling and pain and, on rare occasions, to life-threatening blood clots.

JON KRAUSE (*scales*); JASON LEE, SOURCE: BALTIMORE LONGITUDINAL STUDY OF AGING (*human body*)

cause our slow-paced metabolism differs greatly from that of organisms in which this strategy has already been tested.

Dramatic extension of life span has indeed been achieved in worms, flies and mice. These animals, with their short-lived, fast-burn biology, have an urgent need to manage their metabolism in a way that adapts rapidly to changing circumstances. In nematode worms, for example, most of the more spectacular effects on life span result from mutations that evolved to allow the worms to switch their development to a stress-resistant form whenever they find themselves in a bad environment and potentially required to make a long trek to find better living conditions. We humans, in any case, may not have the same flexibility in altering our own metabolic control. Immediate metabolic effects, of course, occur in humans who undergo voluntary dietary restriction, but only time—and many hungry years—will tell if these have any beneficial impact on the aging process and, in particular, on longevity. The goal of gerontology research in humans, however, is always improving health at the end of life, rather than achieving Methuselean life spans.

One other thing is also very clear: the longer-lived worms, flies and mice still undergo the aging process. Aging happens because damage still accumulates and in time leads to the breakdown of healthy functions of the body. Therefore, if we want our end to be actually better, we need to look elsewhere. In particular, we need to focus on figuring out how to safely limit or reverse the buildup of damage that leads eventually to

© 2015 Scientific American

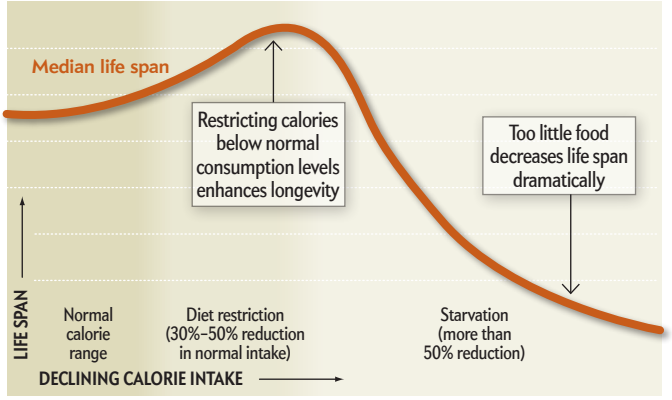
Can We Slow Aging?

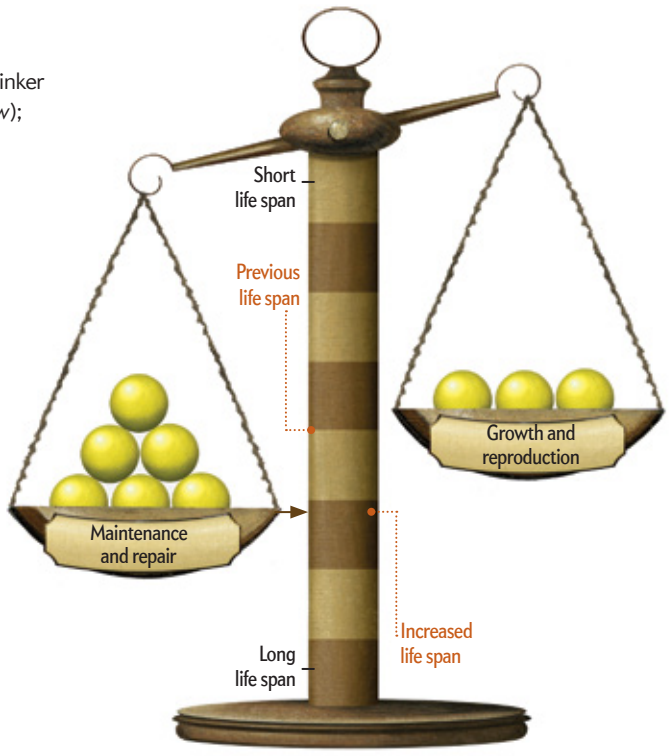
No one yet knows how to slow human aging. But basic research into the process might eventually yield longevity drugs. Some compounds might tinker with cell metabolism (energy use) to mimic benefits seen in animals (*below*); others might change the way damaged cells behave (*opposite page*).

Lean and Long-Lived

Certain therapies might redirect cell metabolism, tilting the scale toward maintenance and repair functions and away from reproduction, thereby keeping bodily organs healthy longer. Calorie restriction lengthens the median life span of flies, worms and mice over that of animals eating a normal diet (*graph*). It is unclear yet whether caloric restriction can work in humans.

Restricting Calories Enhances Life Span in Animals


Median life span
Restricting calories below normal consumption levels enhances longevity
Too little food decreases life span dramatically
LIFE SPAN
Normal calorie range
Diet restriction (30%–50% reduction in normal intake)
Starvation (more than 50% reduction)
DECLINING CALORIE INTAKE



Restricting Calories Affects Energy Allocation

JON KRAUSE (*scales and cells*); LUCY READING-IKKANDA, SOURCE: "EXTENDING HEALTHY LIFE SPAN—FROM YEAST TO HUMANS," BY LUIGI FONTANA ET AL., IN *SCIENCE*, VOL. 328; APRIL 16, 2010 (*graph*)

age-related frailty, disability and disease. This goal represents a huge challenge and calls for some of the most demanding of today's interdisciplinary research.

NO SIMPLE ANSWERS

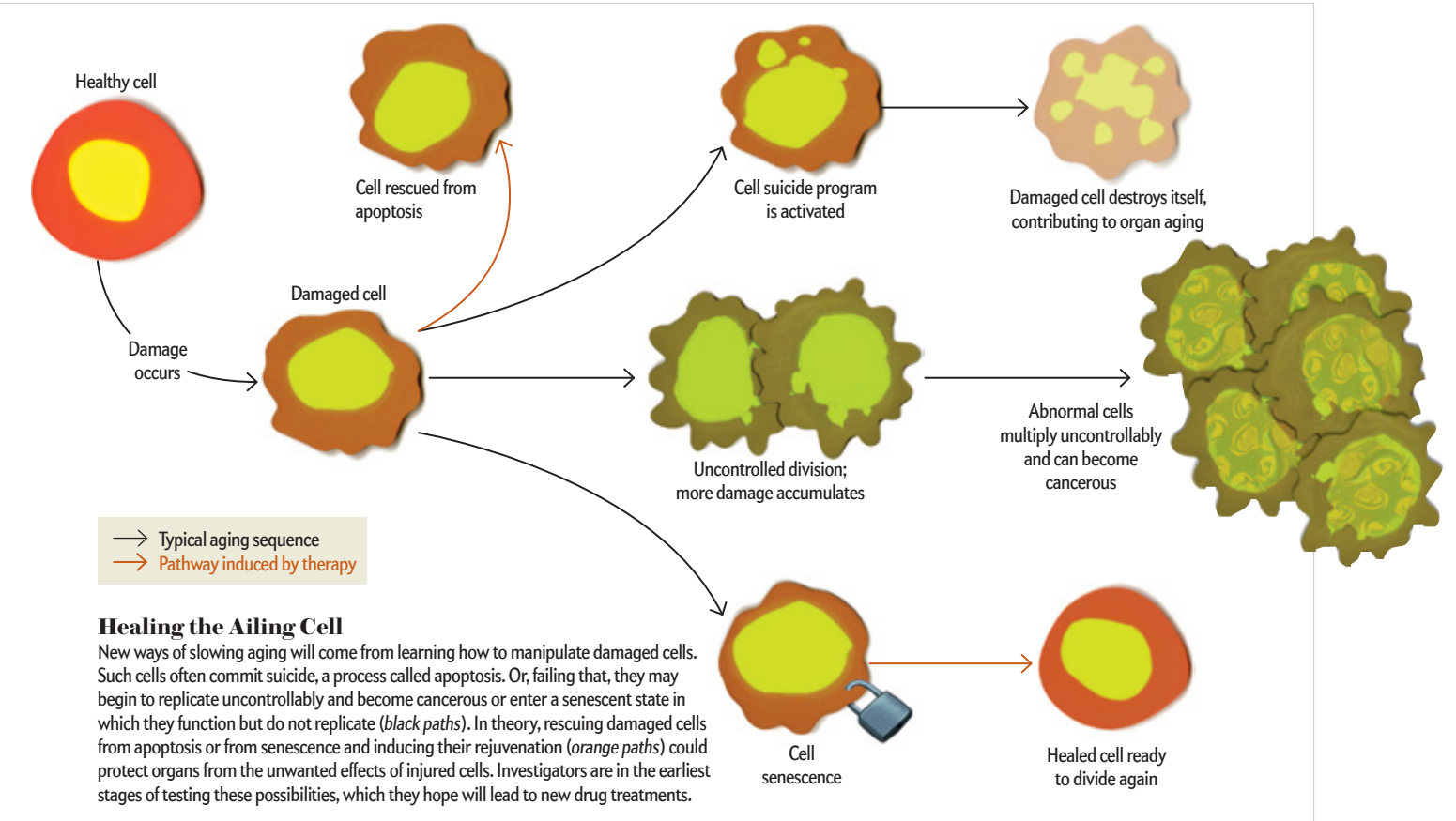
AGING IS COMPLICATED. It affects the body at all levels, from molecules to cells to organs. It also involves multiple kinds of molecular and cellular damage. And although it is true that, in general, this damage accumulates with age and occurs slower in some cell types than in others (depending on the efficiency of the repair systems), injury to any given cell occurs randomly, and the extent can differ even in two cells of the same type in an individual. Thus, all individuals age and die, but the process varies considerably—more confirmation that aging does not stem from a genetic program that specifies how quickly we become frail and die. To understand aging in enough detail to intervene in a suitably targeted fashion that stops or slows the death of selected kinds of cells, we need to know the nature of the molecular defects that drive the aging process at the cellular level. How many of these flaws must accrue before the cell can no longer function? How many defective cells need to accumulate in a given organ before it shows signs of disease? And if we agree that some organs are more important to target than others, how do we deliver the necessary precision?

It may be possible to combat aging by altering important mechanisms that cells use to counteract the buildup of damage. One way that a cell responds to too much wear and tear is simply to kill itself. At one time, scientists viewed this cellular suicide process, technically called apoptosis, as evidence that aging adheres to a genetic program. In aged tissues the frequency of cells killing themselves increases, and this process does indeed contribute to aging. But we now know that apoptosis acts chiefly as a survival mechanism that protects the larger body from injured cells that could potentially cause trouble, notably ones that have become malignant.

Apoptosis happens more in old organs because their cells have suffered more insults. Remember, though, that in nature animals rarely live long enough to grow old. Apoptosis evolved to deal with damaged cells in younger organs, when many fewer would need to be eliminated. If too many cells die, an organ fails or becomes debilitated. So apoptosis is good and bad—good when it deletes potentially dangerous cells, bad when it deletes too many. Nature cares more about survival of the young than managing decline in old age, so not all apoptosis might be strictly necessary in our later years. In some diseases, such as stroke, researchers hope that by suppressing apoptosis in the less damaged tissue, the resulting loss of cells may be reduced, thereby aiding recovery.

Instead of dying, hurt cells that are normally able to reproduce may take a less extreme course and simply stop dividing, a fate known as replicative senescence. More than 50 years ago Leonard Hayflick, now at the University of California, San Francisco, discovered that cells tend to divide a set number of times—now called the Hayflick limit—and then stop. Later work showed

© 2015 Scientific American


Healthy cell
Cell rescued from apoptosis
Cell suicide program is activated
Damaged cell destroys itself, contributing to organ aging
Damaged cell
Damage occurs
Uncontrolled division; more damage accumulates
Abnormal cells multiply uncontrollably and can become cancerous
Typical aging sequence
Pathway induced by therapy
Cell senescence
Healed cell ready to divide again

Healing the Ailing Cell

New ways of slowing aging will come from learning how to manipulate damaged cells. Such cells often commit suicide, a process called apoptosis. Or, failing that, they may begin to replicate uncontrollably and become cancerous or enter a senescent state in which they function but do not replicate (*black paths*). In theory, rescuing damaged cells from apoptosis or from senescence and inducing their rejuvenation (*orange paths*) could protect organs from the unwanted effects of injured cells. Investigators are in the earliest stages of testing these possibilities, which they hope will lead to new drug treatments.

that they often stop dividing when the caps, or telomeres, that protect the ends of chromosomes erode too much. But other details of how cell senescence sets in remained obscure.

A few years ago, though, my colleagues and I made an exciting discovery. We found that each cell has highly sophisticated molecular circuitry that monitors the level of damage both in its DNA and in its energy-forming units known as mitochondria. When the amount of damage passes some threshold, the cell locks itself into a state where it can still perform useful functions in the body but can never divide again. As with apoptosis, nature's bias toward the survival of the young probably means that not all these lockdowns are strictly necessary. But if we are to unpick the locks and so restore some division capacity to aged cells, without unleashing the threat of cancer, we need to understand very thoroughly just how cell senescence works.

The demanding science needed to make this discovery required a multidisciplinary team, including molecular biologists, biochemists, mathematicians and computer scientists, as well as state-of-the-art instruments for imaging the damage in living cells. Where such discoveries might lead we do not yet know, but it is through studies of this kind that we can hope to identify novel drugs able to combat age-related diseases in completely new ways and thereby shorten the period of chronic illness experienced at the end of life. The difficulty of this type of basic research means that many years, perhaps decades, may pass before these drugs come to market.

Using the science of aging to improve the end of life represents a challenge, perhaps the greatest yet to face medical science. Solutions will not come easily, despite the claims made by the merchants of immortality who assert that caloric restriction or dietary supplements, such as resveratrol, may allow us to live longer. The greatest human ingenuity will be needed to meet this challenge. I believe we can and will develop treatments targeted at easing our final years. But when the end arrives, each of us—alone—will need to come to terms with our own mortality. All the more reason then to focus on living—on making the most of the time of our lives, because no magic elixir will save us. SA

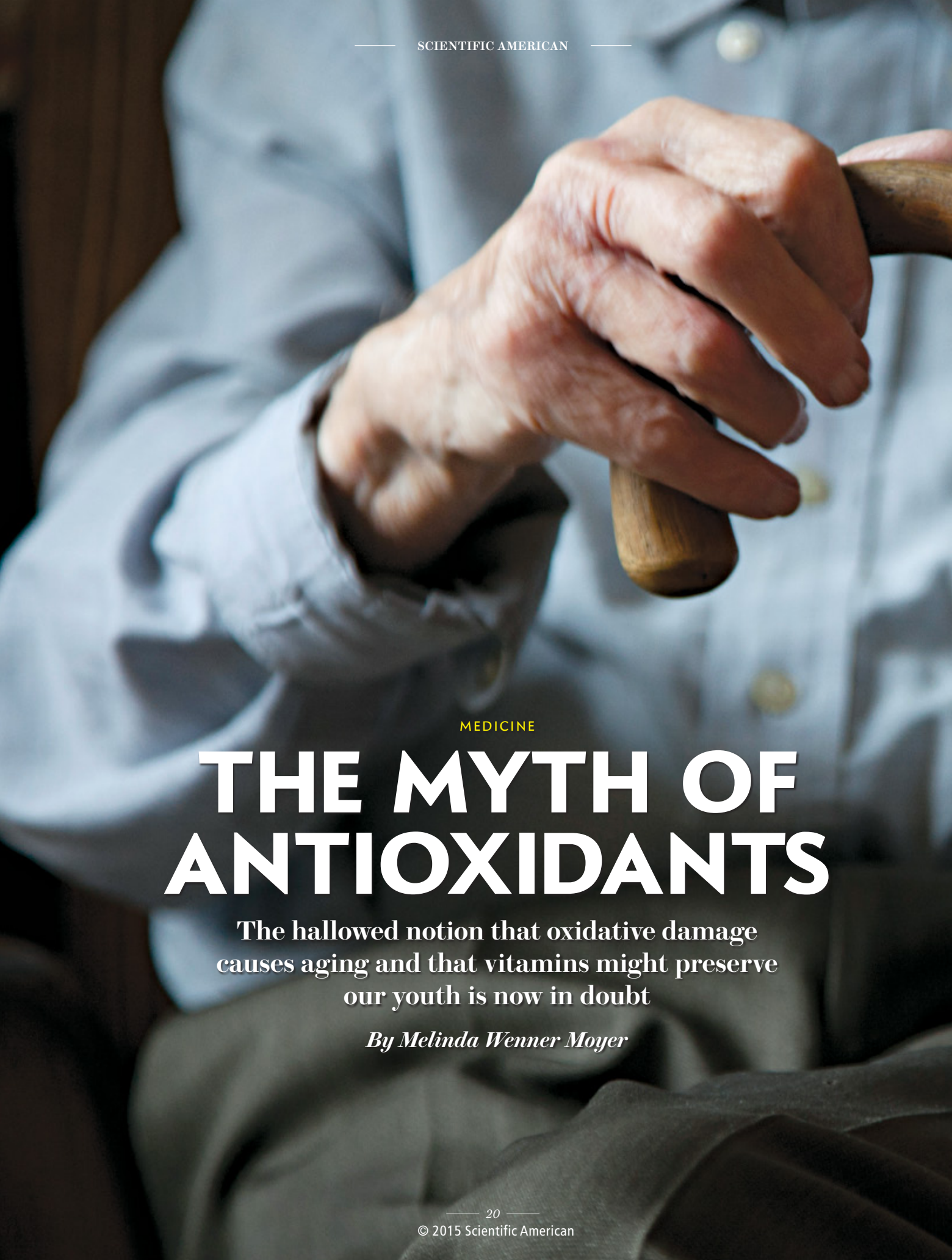
Thomas Kirkwood is at the Newcastle University Institute for Ageing in England, where he was director from 2004 to 2011. His books include the award-winning *Time of Our Lives: The Science of Human Aging,* written for a general readership, and *Chance, Development and Aging* (with Caleb E. Finch) mapping out how intrinsic chance, as well as genes and environment, shapes the way the body grows, develops and ages.

MORE TO EXPLORE

How and Why We Age. Leonard Hayflick. Ballantine Books, 1994.
Understanding Ageing. Robin Holliday. Cambridge University Press, 1995.
Why We Age: What Science Is Discovering about the Body's Journey through Life. Steven N. Austad. John Wiley and Sons, 1999.
Understanding Ageing from an Evolutionary Perspective. T. B. Kirkwood in *Journal of Internal Medicine,* Vol. 263, No. 2, pages 117–127; February 2008.
The End of Age. Thomas Kirkwood. BBC Reith Lectures. www.bbc.co.uk/radio4/reith2001

scientificamerican.com/magazine/sa

© 2015 Scientific American



MEDICINE

THE MYTH OF ANTIOXIDANTS

The hallowed notion that oxidative damage causes aging and that vitamins might preserve our youth is now in doubt

By Melinda Wenner Moyer

© 2015 Scientific American

SECRETS OF STAYING YOUNG

© 2015 Scientific American

DAVID GEMS'S LIFE WAS TURNED UPSIDE DOWN IN 2006 BY A GROUP OF WORMS THAT kept on living when they were supposed to die. As assistant director of the Institute of Healthy Aging at University College London, Gems regularly runs experiments on *Caenorhabditis elegans,* a roundworm that is often used to study the biology of aging. In this case, he was testing the idea that a buildup of cellular damage caused by oxidation—technically, the chemical removal of electrons from a molecule by highly reactive compounds, such as free radicals—is the main mechanism behind aging. According to this theory, rampant oxidation mangles more and more lipids, proteins, snippets of DNA and other key components of cells over time, eventually compromising tissues and organs and thus the functioning of the body as a whole.

Gems genetically engineered the roundworms so they no longer produced certain enzymes that act as naturally occurring antioxidants by deactivating free radicals. Sure enough, in the absence of the antioxidants, levels of free radicals in the worms skyrocketed and triggered potentially damaging oxidative reactions throughout the worms' bodies.

Contrary to Gems's expectations, however, the mutant worms did not die prematurely. Instead they lived just as long as normal worms did. The researcher was mystified. "I said, 'Come on, this can't be right,'" he recalls. "'Obviously something's gone wrong here.'" He asked another investigator in his laboratory to check the results and do the experiment again. Nothing changed. The experimental worms did not produce these particular antioxidants; they accumulated free radicals as predicted, and yet they did not die young—despite suffering extreme oxidative damage.

Other scientists were finding similarly confounding results in different lab animals. In the U.S., Arlan Richardson, director of the Barshop Institute for Longevity and Aging Studies at the University of Texas Health Science Center in San Antonio, genetically engineered 18 different strains of mice, some of which produced more of certain antioxidant enzymes than normal and some of which produced fewer of them than normal. If the damage caused by free radical production and subsequent oxidation was responsible for aging, then the mice with extra antioxidants in their bodies should have lived longer than the mice missing their antioxidant enzymes. Yet "I watched those goddamn life span curves, and there was not an inch of difference between them," Richardson says. He published his increasingly bewildering results in a series of papers between 2001 and 2009.

Meanwhile, a few doors down the hall from Richardson, physiologist Rochelle Buffenstein has spent more than 10 years trying to understand why the longest-living rodent, the naked mole rat, is able to survive up to 25 to 30 years—around eight times longer than a similarly sized mouse. Buffenstein's experiments have shown that naked mole rats possess lower levels of natural antioxidants than mice and accumulate more oxidative damage to their tissues at an earlier age than other rodents. Yet paradoxically, they live virtually disease-free until they die at a very old age.

To proponents of the long-standing oxidative damage theory of aging, these findings are nothing short of heretical. They are, however, becoming less the exception and more the rule. Over

IN BRIEF

For decades researchers assumed that highly reactive molecules called free radicals caused aging by damaging cells and thus undermining the functioning of tissues and organs.

Recent experiments, however, show that increases in certain free radicals in mice and worms correlate with longer life span. Indeed, in some circumstances, free radicals seem to signal cellular repair networks.

If these results are confirmed, they may suggest that taking antioxidants in the form of vitamins or other supplements can do more harm than good in otherwise healthy individuals.

Aging does not seem to be a process with a single cause and a single cure; it is even more complicated than researchers thought.

PRECEDING PAGES: THOMAS BORN *Corbis*

© 2015 Scientific American

the course of the past decade, many experiments designed to further support the idea that free radicals and other reactive molecules drive aging have instead directly challenged it. What is more, it seems that in certain amounts and situations, these high-energy molecules may not be dangerous but useful and healthy, igniting intrinsic defense mechanisms that keep our bodies in tip-top shape. These ideas not only have drastic implications for future antiaging interventions, but they also raise questions about the common wisdom of popping high doses of antioxidant vitamins. If the oxidative-damage theory is wrong, then researchers may need to revise their understanding of what healthy aging looks like on the molecular level.

"The field of aging has been gliding along on this set of paradigms, ideas about what aging is, that to some extent were kind of plucked out of the air," Gems says. "We should probably be looking at other theories as well and considering, fundamentally, that we might have to look completely differently at biology."

THE BIRTH OF A RADICAL THEORY

THE OXIDATIVE DAMAGE, or free radical, theory of aging can be traced back to Denham Harman, who found his true calling in December 1945, thanks to the *Ladies' Home Journal*. His wife, Helen, brought a copy of the magazine home and pointed out an article on the potential causes of aging, which he read. It fascinated him.

Back then, the 29-year-old chemist was working at Shell Development, the research arm of Shell Oil, and he did not have much time to ponder the issue. Yet nine years later, after graduating from medical school and completing his training, he took a job as a research associate at the University of California, Berkeley, and began contemplating the science of aging more seriously. One morning while sitting in his office, he had an epiphany—"you know just 'out the blue,'" he recalled in a 2003 interview: aging must be driven by free radicals.

Although free radicals had never before been linked to aging, it made sense to Harman that they might be the culprit. For one thing, he knew that ionizing radiation from x-rays and radioactive bombs, which can be deadly, sparks the production of free radicals in the body. Studies at

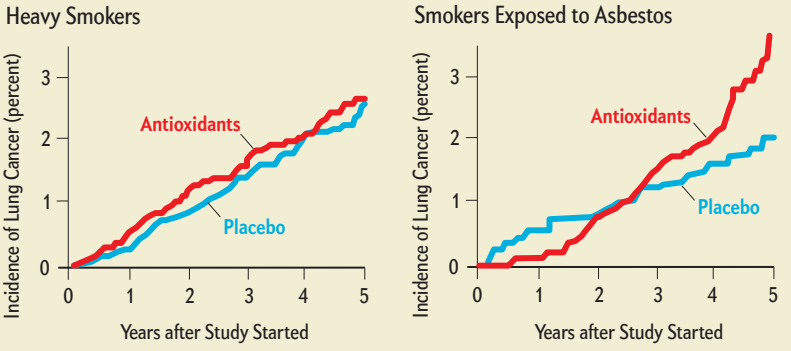
EVIDENCE FROM HUMANS

When Vitamins Kill

Epidemiological studies show that people who eat lots of fruits and vegetables, which are rich in vitamins and other antioxidants, tend to live longer and are less likely to develop cancer compared with those who do not. So it seemed obvious that supplementing diet with antioxidants should lead to better health. But the results of the most rigorously designed studies do not support that assumption. Indeed, the evidence shows that some people who take certain supplements are actually more likely to develop life-threatening illnesses, such as lung cancer and heart disease.

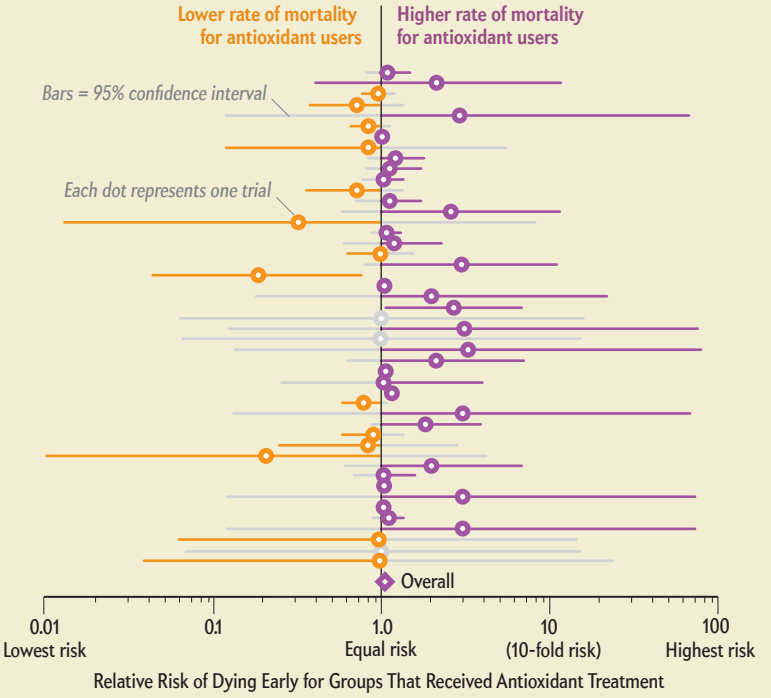
Early Signs That Antioxidants Can Spell Trouble

A 1996 study of some 18,000 men and women found 28 percent more lung cancers and 17 percent more deaths in a group that was given beta-carotene and retinol compared with people who did not receive the antioxidants. The increased risk became clear after 18 months, particularly in heavy smokers, and was strongest among smokers who had been exposed to asbestos, a known carcinogen.



Bottom Line: Taking Some Vitamins Can Shorten Life Span

In 2007 researchers reviewed 68 of the most scientifically rigorous studies of vitamins and reported that pooling the data from the 47 trials with the least scientific bias resulted in a 5 percent increase in the rate of early death. Further analysis linked the increased risk to beta-carotene, vitamin A and vitamin E.



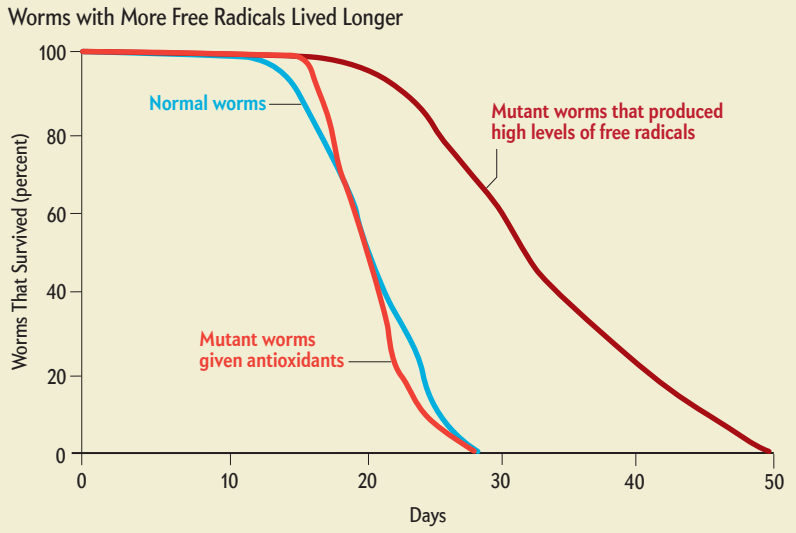
SOURCE: "RISK FACTORS FOR LUNG CANCER AND FOR INTERVENTION EFFECTS IN CARET, THE BETA-CAROTENE AND RETINOL EFFICACY TRIAL," BY GILBERT S. OMENN ET AL., IN *JOURNAL OF THE NATIONAL CANCER INSTITUTE*, VOL. 88, NO. 21; NOVEMBER 6, 1996 (*top*); "MORTALITY IN RANDOMIZED TRIALS OF ANTIOXIDANT SUPPLEMENTS FOR PRIMARY AND SECONDARY PREVENTION: SYSTEMATIC REVIEW AND META-ANALYSIS," BY GORAN BJELAKOVIC ET AL., IN *JAMA*, VOL. 297, NO. 8; FEBRUARY 28 (*bottom*)

© 2015 Scientific American

EVIDENCE FROM ANIMALS

Insight from Mutant Worms

Rather than causing aging (through oxidative chemical reactions that trigger cellular damage), some free radicals may prove beneficial. One possibility, supported by the work of Siegfried Hekimi and Wen Yang, is that a certain number of free radicals stimulate an organism's internal repair mechanisms to get to work. In their experiment on roundworms, published in 2010, the researchers genetically modified a group of worms so that they produced high levels of certain free radicals. Much to their surprise, the mutant worms lived longer than the normal worms. When the investigators fed antioxidants to the mutant worms, their longevity advantage disappeared.



SECRETS OF STAYING YOUNG

the time suggested that diets rich in food-based antioxidants muted radiation's ill effects, suggesting—correctly, as it turned out—that the radicals were a cause of those effects. Moreover, free radicals were normal by-products of breathing and metabolism and built up in the body over time. Because both cellular damage and free radical levels increased with age, free radicals probably caused the damage that was responsible for aging, Harman thought—and antioxidants probably slowed it.

Harman started testing his hypothesis. In one of his first experiments, he fed mice antioxidants and showed that they lived longer. (At high concentrations, however, the antioxidants had deleterious effects.) Other scientists soon began testing it, too. In 1969 researchers at Duke University discovered the first antioxidant enzyme produced inside the body—superoxide dismutase—and speculated that it evolved to counter the deleterious effects of free radical accumulation. With these new data, most biologists began accepting the idea. "If you work in aging, it's like the air you breathe is the free radical theory," Gems says. "It's ubiquitous, it's in every textbook. Every paper seems to refer to it either indirectly or directly."

Still, over time scientists had trouble replicating some of Harman's experimental findings. By the 1970s "there wasn't a robust demonstration that feeding animals antioxidants really had an effect on life span," Richardson says. He assumed that the conflicting experiments—which had been done by other scientists—simply had not been controlled very well. Perhaps the animals could not absorb the antioxidants that they had been fed, and thus the overall level of free radicals in their blood had not changed. By the 1990s, however, genetic advances allowed scientists to test the effects of antioxidants in a more precise way—by directly manipulating genomes to change the amount of antioxidant enzymes animals were capable of producing. Time and again, Richardson's experiments with genetically modified mice showed that the levels of free radical molecules circulating in the animals' bodies—and subsequently the amount of oxidative damage they endured—had no bearing on how long they lived. More recently, Siegfried Hekimi, a biologist at McGill University, has bred roundworms that overproduce a specific free radical known as superoxide. "I thought they were going to help us prove the theory that oxidative stress causes aging," says Hekimi, who had predicted that the worms would die young. Instead he reported in a 2010 paper in *PLOS Biology* that the engineered worms did not develop high levels of oxidative damage and that they lived, on average, 32 percent *longer* than normal worms. Indeed, treating these genetically modified worms with the antioxidant vitamin C prevented this increase in life span. Hekimi speculates that superoxide acts not as a destructive molecule but as a protective signal in the worms' bodies, turning up the expression of genes that help to repair cellular damage.

In a follow-up experiment, Hekimi exposed normal worms, from birth, to low levels of a common weed-controlling herbicide that initiates free radical production in animals as well as plants. In the same 2010 paper he reported the counterintuitive result: the toxin-bathed worms lived 58 percent longer than untreated worms. Again, feeding the worms antioxidants quenched the toxin's beneficial effects. Finally, in April 2012, he and his colleagues showed that knocking out, or deactivating, all five of the genes that code for superoxide dismutase enzymes in worms has virtually no effect on worm life span.

Do these discoveries mean that the free radical theory is flat-out wrong? Simon Melov, a biochemist at the Buck Institute for Research on Aging in Novato, Calif., believes that the issue is unlikely to be so simple; free radicals may be beneficial in some contexts and dangerous in others. Large amounts of oxidative damage have indisputably been shown to cause cancer and organ damage, and plenty of evidence indicates that oxidative damage plays a role in the development of some chronic conditions, such as heart disease. In addition, researchers at the University of Washington have demonstrated that mice live longer when they are genetically engineered to produce high levels of an antioxidant known as catalase. Saying that something, like

SOURCE: "A MITOCHONDRIAL SUPEROXIDE SIGNAL TRIGGERS INCREASED LONGEVITY IN *CAENORHABDITIS ELEGANS*," BY WEN YANG AND SIEGFRIED HEKIMI, IN *PLOS BIOLOGY*, VOL. 8, NO. 12; DECEMBER 2010

© 2015 Scientific American

oxidative damage, contributes to aging in certain instances, however, is "a very different thing than saying that it drives the pathology," Melov notes. Aging probably is not a monolithic entity with a single cause and a single cure, he argues, and it was wishful thinking to ever suppose it was one.

SHIFTING PERSPECTIVE

ASSUMING FREE RADICALS accumulate during aging but do not necessarily cause it, what effects *do* they have? So far that question has led to more speculation than definitive data.

"They're actually part of the defense mechanism," Hekimi asserts. Free radicals might, in some cases, be produced in response to cellular damage—as a way to signal the body's own repair mechanisms, for example. In this scenario, free radicals are a consequence of age-related damage, not a cause of it. In large amounts, however, Hekimi says, free radicals may create damage as well.

The general idea that minor insults might help the body withstand bigger ones is not new. Indeed, that is how muscles grow stronger in response to a steady increase in strain. Many occasional athletes, on the other hand, have learned from painful firsthand experience that an abrupt increase in the physical demands they place on their body after a long week of sitting at an office desk is instead almost guaranteed to lead to pulled calves and hamstrings, among other significant injuries.

In 2002 researchers at the University of Colorado Boulder briefly exposed worms to heat or to chemicals that induced the production of free radicals, showing that these stressors each boosted the worms' ability to survive larger insults later. The interventions also increased the worms' life expectancy by 20 percent. It is unclear how these interventions affected overall levels of oxidative damage, however, because the investigators did not assess these changes. In 2010 researchers at the University of California, San Francisco, and Pohang University of Science and Technology in South Korea reported in *Current Biology* that some free radicals turn on a gene called *HIF-1* that is itself responsible for activating a number of genes involved in cellular repair, including one that helps to repair mutated DNA.

Free radicals may also explain in part why exercise is beneficial. For years researchers assumed that exercise was good in spite of the fact that it produces free radicals, not because of it. Yet in a 2009 study published in the *Proceedings of the National Academy of Sciences USA,* Michael Ristow, then a nutrition professor at the Friedrich Schiller University of Jena in Germany, and his colleagues compared the physiological profiles of exercisers who took antioxidants with exercisers who did not. Echoing Richardson's results in mice, Ristow found that the exercisers who did not pop vitamins were healthier than those who did; among other things, the unsupplemented athletes showed fewer signs that they might develop type 2 diabetes.

Research by Beth Levine, a microbiologist at the University of Texas Southwestern Medical Center, has shown that exercise also ramps up a biological process called autophagy (from the Greek for "self-eating"), in which cells recycle worn-out bits of proteins and other subcellular pieces. The tool used to digest and disassemble the old molecules: free radicals. Just to complicate matters a bit, however, Levine's research indicates that autophagy also reduces the overall level of free radicals, suggesting that the types and amounts of free radicals in different parts of the cell may play various roles, depending on the circumstances.

THE ANTIOXIDANT MYTH

IF FREE RADICALS are not always bad, then their antidotes, antioxidants, may not always be good—a worrisome possibility given that 52 percent of Americans take considerable doses of antioxidants daily, such as vitamin E and beta-carotene, in the form of multivitamin supplements. In 2007 the *Journal of the American Medical Association* published a systematic review of 68 clinical trials, which concluded that antioxidant supplements do not reduce risk of death. When the authors limited their review to the trials that were least likely to be affected by bias—those in which assignment of participants to their research arms was clearly random and neither investigators nor participants knew who was getting what pill, for instance—they found that certain antioxidants were linked to an increased risk of death, in some cases by up to 16 percent.

Several U.S. organizations, including the American Heart Association and the American Diabetes Association, now advise that people should not take antioxidant supplements except to treat a diagnosed vitamin deficiency. "The literature is providing growing evidence that these supplements—in particular, at high doses—do not necessarily have the beneficial effects that they have been thought to," says Demetrius Albanes, a senior investigator at the Nutritional Epidemiology Branch of the National Cancer Institute. Instead, he says, "we've become acutely aware of potential downsides." In a 2013 editorial published in the *Annals of Internal Medicine,* researchers at the Johns Hopkins Bloomberg School of Public Health and other institutions concluded that "the case is closed—supplementing the diet of well-nourished adults with (most) mineral or vitamin supplements has no clear benefit and might even be harmful."

It is hard to imagine, however, that antioxidants will ever fall out of favor completely—or that most researchers who study aging will become truly comfortable with the idea of beneficial free radicals without a lot more proof. Yet slowly, it seems, the evidence is beginning to suggest that aging is far more intricate and complex than Harman (who died in 2014) imagined it to be nearly 60 years ago.

Gems, for one, believes the evidence points to a new theory in which aging stems from the overactivity of certain biological processes involved in growth and reproduction. But no matter what idea (or ideas) scientists settle on, moving forward, "the constant drilling away of scientists at the facts is shifting the field into a slightly stranger, but a bit more real, place," Gems says. "It's an amazing breath of fresh air." SA

Melinda Wenner Moyer is a science writer based in Cold Spring, N.Y. She is also an adjunct assistant professor at the City University of New York Graduate School of Journalism.

MORE TO EXPLORE

Is the Oxidative Stress Theory of Ageing Dead? Viviana I. Pérez et al. in *Biochimica et Biophysica Acta,* Vol. 1970, No. 10, pages 1005–1014; October 2009.

Biology of Aging: Research Today for a Healthier Tomorrow. National Institute on Aging. National Institutes of Health, November 2011. www.nia.nih.gov/health/publication/biology-aging

Alternative Perspectives on Aging in *Caenorhabditis elegans:* Reactive Oxygen Species or Hyperfunction? David Gems and Yila de la Guardia in *Antioxidants & Redox Signaling.* Published online September 24, 2012.

© 2015 Scientific American

KENDRICK BRINSON

WHY WOMEN LIVE LONGER

Stress alone does not explain the longevity gap

By Thomas Kirkwood

If there are any men left who still believe that women are the weaker sex, it is long past time for them to think again. With respect to that most essential proof of robustness—the power to stay alive—women are tougher than men from birth through to extreme old age. The average man may run a 100-meter race faster than the average woman and lift heavier weights. But nowadays women outlive men by about five to six years. By age 85 there are roughly six women to every four men. At age 100 the ratio is more than two to one. And by age 122—the current world record for human longevity—the score stands at one-nil in favor of women.

So why do women live longer than men? One idea is that men drive themselves to an early grave with all the hardship and stress of their working lives. If this were so, however, then in these days of greater gender equality, you might expect the mortality gap would vanish or at least diminish. Yet there is little evidence that this is happening. Women today still outlive men by about as much as their stay-at-home mothers outlived their office-going fathers a generation ago. Furthermore, who truly believes that men's work lives back then were so much more damaging to their health than women's home lives? Just think about the stresses and strains that have always existed in the traditional roles of women: a woman's life in a typical household can be just as hard as a man's. Indeed, statistically speaking, men get a much better deal out of marriage than their wives—married men tend to live many years longer than single men, whereas married women live only a little bit longer than single women. So who actually has the easier life?

It might be that women live longer because they develop healthier habits than men—for example, smoking and drinking less and choosing a better diet. But the number of women who smoke is growing, and plenty of others drink and eat unhealthy foods. In any case, if women are so healthy, why is it that despite their longer lives, women spend more years of old age in poor health than men do? The lifestyle argument therefore does not answer the question either.

As an experimental gerontologist, I approach this issue

© 2015 Scientific American

from a wider biological perspective, by looking at other animals. It turns out that the females of most species live longer than the males, which suggests that the explanation for the difference within humans might lie deep in our biology.

Many scientists believe that the aging process is caused by the gradual buildup of a huge number of individually tiny faults—some damage to a DNA strand here, a deranged protein molecule there, and so on. This degenerative buildup means that the length of our lives is regulated by the balance between how fast new damage strikes our cells and how efficiently this damage is corrected. The body's mechanisms to maintain and repair our cells are wonderfully effective—which is why we live as long as we do—but these mechanisms are not perfect. Some of the damage passes unrepaired and accumulates as the days, months and years pass by. We age because our bodies keep making mistakes.

We might well ask why our bodies do not repair themselves better. Actually we probably could fix damage better than we do already. In theory at least, we might even do it well enough to live forever. The reason we do not, I believe, is because it would have cost more energy than it was worth when our aging process evolved long ago, when our hunter-gatherer ancestors faced a constant struggle against hunger. Under the pressure of natural selection to make the best use of scarce energy supplies, our species gave higher priority to growing and reproducing than to living forever. Our genes treated the body as a short-term vehicle, to be maintained well enough to grow and reproduce, but not worth a greater investment in durability when the chance of dying an accidental death was so great. In other words, genes are immortal, but the body—what the Greeks called *soma*—is disposable.

Or at least that is the idea I proposed in the late 1970s. Since then, the evidence to support this disposable soma theory has grown significantly [see my article "Why Can't We Live Forever?" on page 12]. In my own laboratory some years ago we showed that longer-lived animals have better maintenance and repair systems than short-lived animals do. The longer-lived animals are also the smarter ones, or the bigger ones, or the ones like birds and bats that evolved adaptations such as wings to make their lives safer. If you can avoid the hazards of the environment for a bit longer by flying away from danger or being cleverer or bigger, then the body is correspondingly a bit less disposable, and it pays to spend more energy on repair.

Could it be that women live longer because they are less disposable than men? This notion, in fact, makes excellent biological sense. In humans, as in most animal species, the state of the female body is very important for the success of reproduction. The fetus needs to grow inside the mother's womb, and the infant needs to suckle at her breast. So if the female animal's body is too much weakened by damage, there is a real threat to her chances of making healthy offspring. The man's reproductive role, on the other hand, is less directly dependent on his continued good health.

It is too extreme to say that for all biology cares, males need only to attract a mate and then can pretty much die. A study of children in Tanzania, for example, showed that children who lost a father before the age of 15 tended to be a little shorter than their peers, and height is a reasonably good proxy for health. But children who lost a mother fared even worse—they were shorter, poorer and did not live as long as fatherless orphans. From an evolutionary point of view, however, the drivers of mating success for males are generally not the drivers of longevity. In fact, high levels of testosterone, which boost male fertility, are quite bad for long-term survival.

FOUNTAIN OF YOUTH: Not only is she likely to live longer than he does, she will help him live longer, too.

Women may still struggle to achieve equality in many spheres of life. To be less disposable, however, is a blessing that offers some compensation. There is evidence from studies in rodents that cells in a female body do repair damage better than in the body of a male and that surgical removal of the ovaries eliminates this difference. As many dog and cat owners can attest, neutered male animals often live longer than their intact counterparts. Indeed, the evidence supports the notion that male castration might be the ticket to a longer life.

Might the same be true of humans? Eunuchs were once members of the elite in many societies. In China, boys were castrated to enable them to serve the emperor without the risk of impregnating his concubines. In Europe, such extreme practices were used to retain the singing qualities of boys as they moved into adolescence.

The historical record is not good enough to determine if eunuchs tend to outlive normal healthy men, but some sad records suggest that they do. A number of years ago castration of men in institutions for the mentally disturbed was surprisingly commonplace. In one study of several hundred men at an unnamed institution in Kansas, the castrated men were found to live on average 14 years longer than their uncastrated fellows. Nevertheless, I doubt that many men—myself included—would choose such a drastic remedy to buy a few extra years. SA

Thomas Kirkwood is at the Newcastle University Institute for Ageing in England, where he was director from 2004 to 2011, and is author of *Time of Our Lives: The Science of Human Aging.*

KENDRICK BRINSON

© 2015 Scientific American

ANTHROPOLOGY

THE EVOLUTION OF GRANDPARENTS

The rise of senior citizens may have played a big role in the success of our species

By Rachel Caspari

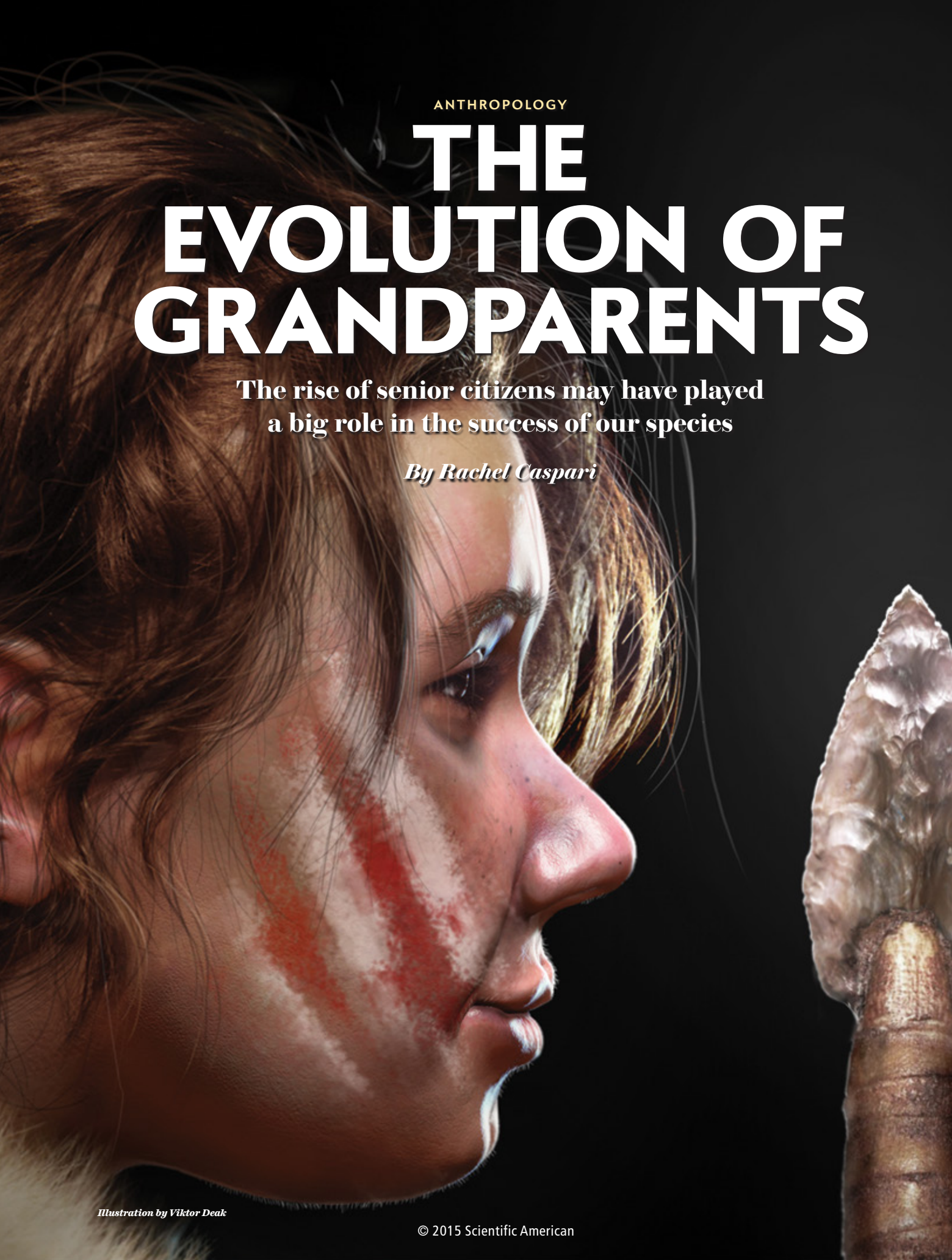


Illustration by Viktor Deak

© 2015 Scientific American

© 2015 Scientific American

DURING THE SUMMER OF 1963, WHEN I WAS SIX YEARS OLD, MY FAMILY TRAVELED from our home in Philadelphia to Los Angeles to visit my maternal relatives. I already knew my grandmother well: she helped my mother care for my twin brothers, who were only 18 months my junior, and me. When she was not with us, my grandmother lived with her mother, whom I met that summer for the first time. I come from a long-lived family. My grandmother was born in 1895 and her mother in the 1860s; both lived almost 100 years. We stayed with the two matriarchs for several weeks. Through their stories, I learned about my roots and where I belonged in a social network spanning four generations. Their reminiscences personally connected me to life at the end of the Civil War and the Reconstruction era and to the challenges my ancestors faced and the ways they persevered.

My story is not unique. Elders play critical roles in human societies around the globe, conveying wisdom and providing social and economic support for the families of their children and larger kin groups. In our modern era, people routinely live long enough to become grandparents. But this was not always the case. When did grandparents become prevalent, and how did their ubiquity affect human evolution?

Research my colleagues and I have been conducting indicates that grandparent-aged individuals became common relatively recently in human prehistory and that this change came at about the same time as cultural shifts toward distinctly modern behaviors—including a dependence on sophisticated symbol-based communication of the kind that underpins art and language. These findings suggest that living to an older age had profound effects on the population sizes, social interactions and genetics of early modern human groups and may explain why they were more successful than archaic humans, such as the Neandertals.

LIVE FAST, DIE YOUNG

THE FIRST STEP in figuring out when grandparents became a fixture in society is assessing the typical age breakdown of past populations—what percent were children, adults of childbearing age and parents of those younger adults. Reconstructing the demography of ancient populations is tricky business, however. For one thing, whole populations are never preserved in the fossil record. Rather paleontologists tend to recover fragments of individuals. For another, early humans did not necessarily mature at the same rate as modern humans. In fact, maturation rates differ even among contemporary human populations. But a handful of sites have yielded high enough numbers of human fossils in the same layers of sediment that scientists can confidently assess the age at death of the remains—which is key to understanding the makeup of a prehistoric group.

A rock-shelter located in the town of Krapina in Croatia, about 40 kilometers northwest of the city of Zagreb, is one such site. More than a century ago Croatian paleontologist Dragutin Gorjanović-Kramberger excavated and described the fragmentary remains of perhaps as many as 70 Neandertal individuals there, most of which came from a layer dated to about 130,000 years ago. The large number of fossils found close to one another, the apparently rapid accumulation of the sediments at the site and the fact that some of the remains share distinctive, genetically determined features all indicate that the Krapina bones approximate the remains of a single population of Neandertals. As often happens in the fossil record, the best-preserved remains at Krapina are teeth because the high mineral content of teeth protects them from degradation. Fortunately, teeth are also one of the best skeletal elements for determining age at death, which is achieved by analyzing surface wear and age-related changes in their internal structure.

In 1979, before I began my research into the evolution of grandparents, Milford H. Wolpoff of the University of Michigan published a paper, based on dental remains, that assessed how old the Krapina Neandertals were when they died. Molar teeth erupt sequentially. Using one of the fastest eruption schedules observed in modern-day humans as a guide, Wolpoff estimated that the first, second and third molars of Neandertals erupted at ages that rounded to six, 12 and 15, respectively. Wear from chewing accumulates at a steady pace over a lifetime, so when the second molar emerges, the first already has six years of wear on it, and when the third emerges, the second has three years of wear.

Working backward, one can infer, for instance, that a first molar with 15 years of wear on it belonged to a 21-year-old Neandertal, a second molar with 15 years of wear on it belonged to a 27-year-old and a third molar with 15 years of wear on it belonged to a 30-year-old. (These estimates have an uncertainty of plus or minus one year.) This wear-based seriation method for determining age at death, adapted from a technique developed by dental researcher A.E.W. Miles in 1963, works best on samples with large numbers of juveniles, which Krapina has in abun-

IN BRIEF

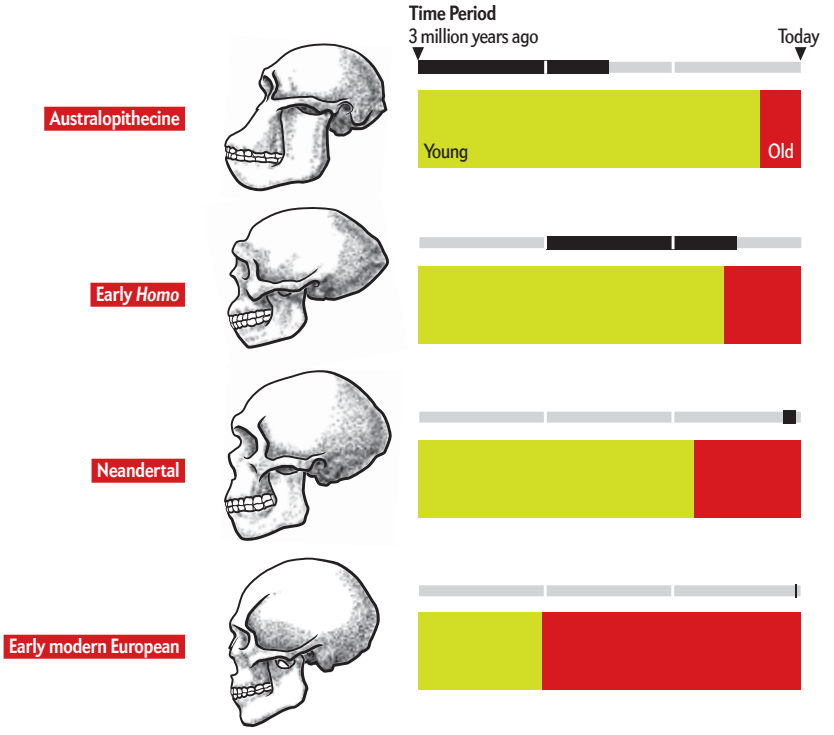
People today typically live long enough to become grandparents, but this was not always the case.
Recent analyses of fossil teeth indicate that grandparents were rare in ancient populations, such as those of the australopithecines and the Neandertals. They first became common around 30,000 years ago, as evidenced by remains of early modern Europeans.
This surge in the number of seniors may have been a driving force for the explosion of new tool types and art forms that occurred in Europe at around the same time. It also may explain how modern humans outcompeted archaic groups such as the Neandertals.

© 2015 Scientific American

FINDINGS

Growing Older

Analyses of the fossilized teeth of hundreds of individuals spanning three million years indicate that living long enough to reach grandparenthood became common relatively late in human evolution. The author and her colleague assessed the proportion of older (grandparent-aged) adults relative to younger adults in four groups of human ancestors—australopithecines, early members of the genus *Homo*, Neandertals and early modern Europeans—and found that the ratio increased only modestly over the course of human evolution until around 30,000 years ago, when it skyrocketed.



dance. The method loses accuracy when applied to the teeth of elderly individuals, whose tooth crowns can be too worn to evaluate reliably and in some cases may even be totally eroded.

Wolpoff's work indicated that the Krapina Neandertals died young. In 2005, a few years after I began researching the evolution of longevity, I decided to take another look at this sample using a novel approach. I wanted to make sure that we were not missing older individuals as a result of the inherent limitations of wear-based seriation. With Jakov Radovčić of the Croatian Natural History Museum in Zagreb, Steven A. Goldstein, Jeffrey A. Meganck and Dana L. Begun, then all at Michigan, and undergraduate students from Central Michigan University, I worked to develop a new nondestructive method—using high-resolution three-dimensional microcomputed tomography (μCT)—to reassess how old the Krapina individuals were when they died. Specifically, we looked at the degree of development of a type of tissue within the tooth called secondary dentin; the volume of secondary dentin increases with age and provides a way to assess how old an individual was at death when the tooth crown is too worn to be a good indicator.

Our initial findings, supplemented with scans provided by the Max Planck Institute for Evolutionary Anthropology in Leipzig, Germany, corroborated Wolpoff's results and validated the wear-based seriation method: the Krapina Neandertals had remarkably high mortality rates; no one there survived past age 30. (This is not to say that Neandertals never lived beyond 30. A few individuals from other sites were around 40 when they died.)

By today's standards, the Krapina death pattern is unimaginable. After all, for most people age 30 is the prime of life. And hunter-gatherers lived beyond 30 in the recent past. Yet the Krapina Neandertals are not unique among early humans. The few other human fossil localities with large numbers of individuals preserved, such as the approximately 600,000-year-old Sima de los Huesos site in Atapuerca, Spain, show similar patterns. The Sima de los Huesos people had very high levels of juvenile and young adult mortality, with no one surviving past 35 and very few living even that long. It is possible that catastrophic events or the particular conditions under which the remains became fossilized somehow selected against the preservation of older individuals at these sites. But the broad surveys of the human fossil record that my colleagues and I have conducted indicate that dying young was the rule, not the exception. To paraphrase words attributed to British philosopher Thomas Hobbes, prehistoric life really was nasty, brutish and short.

RISE OF THE GRANDPARENTS

THIS NEW μCT APPROACH has the potential to provide a high-resolution picture of the ages of older individuals in other fossil human populations. About a decade ago, before we hit on this technique, Sang-Hee Lee of the University of California, Riverside, and I were ready to start looking for evidence of changes in longevity over the course of human evolution. We turned to the best approach available at the time: wear-based seriation.

We faced a daunting challenge, though. Most human fossils do not come from sites, such as Krapina, that preserve so many individuals that the remains can be considered reflective of their larger populations. And the smaller the number of contemporaneous individuals found at a site, the more difficult it is to reliably estimate how old members were when they died because of the statistical uncertainties associated with small samples.

But we realized that we could get at the question of when grandparents started becoming common in another way. Instead of asking how long individuals lived, we asked how many of them lived to be old. That is, rather than focusing on absolute

PORTIA SLOAN ROLLINGS (*skull illustrations*). JEN CHRISTIANSEN (*graphic*). SOURCE: "OLDER AGE BECOMES COMMON LATE IN HUMAN EVOLUTION," BY RACHEL CASPARI AND SANG-HEE LEE, IN *PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES USA*, VOL. 101, NO. 30; JULY 27, 2004

SECRETS OF STAYING YOUNG

© 2015 Scientific American

Culture Comes of Age

A marked increase in adult survivorship starting around 30,000 years ago in Europe may account for the dramatic cultural shift that ensued there as the comparatively simple technology of the Middle Paleolithic gave way to the sophisticated weapons and art of the Upper Paleolithic. Representative artifacts from both cultural traditions are shown here.

Middle Paleolithic
Flint point (*left*) and side scraper (*above*) from Le Moustier, France
Upper Paleolithic
Bone flute from Hohle Fels, Germany
Stone burin from Brassempouy, France
Ceramic Venus figurine from Dolni Vestonice, Czech Republic
ARTIFACTS NOT TO SCALE

ages, we calculated relative ages and asked what proportion of adults survived to the age at which one could first become a grandparent. Our objective was to evaluate changes over evolutionary time in the ratio of older to younger adults—the so-called OY ratio. Among primates, including humans up until very recently, the third molar erupts at about the same time that an individual becomes an adult and reaches reproductive age. Based on data from Neandertals and contemporary hunter-gatherer populations, we inferred that fossil humans got their third molars and had their first child at around age 15. And we considered double that age to mark the beginning of grandparenthood—just as some women today can potentially give birth at age 15 and those women can become grandmothers when their own children reach age 15 and reproduce.

For our purposes, then, any archaic individual judged to be 30 years old or more qualified as an older adult—one old enough to have become a grandparent. But the beauty of the OY ratio approach is that regardless of whether maturation occurred at 10, 15 or 20 years, the number of older and younger individuals in a sample would be unaffected because the start of older adulthood would change accordingly. And because we were only looking to place the fossils in these two broad categories, we could include large numbers of smaller fossil samples in our analysis without worrying about uncertainties in absolute ages.

We calculated the OY ratios for four large aggregates of fossil samples totaling 768 individuals spanning a period of three million years. One aggregate comprised later australopithecines, who lived in Africa from three million to 1.5 million years ago. Another aggregate consisted of early members of our genus, *Homo,* from around the globe who lived between two million and 500,000 years ago. The third group was the European Neandertals from 130,000 to 30,000 years ago. And the last consisted of modern Europeans from the early Upper Paleolithic period, who lived between about 30,000 and 20,000 years ago and left behind sophisticated cultural remains.

Although we expected to find increases in longevity over time, we were unprepared for how striking our results would turn out to be. We observed a small trend of increased longevity over time among all samples, but the difference between earlier humans and the modern humans of the Upper Paleolithic was a dramatic fivefold increase in the OY ratio. Thus, for every 10 young adult Neandertals who died between the ages of 15 and 30, there were only four older adults who survived past age 30; in contrast, for every 10 young adults in the European Upper Paleolithic death distribution, there were 20 potential grandparents. Wondering whether the higher numbers of burials at Upper Paleolithic sites might account for the high number of older adults in that sample, we reanalyzed our Upper Paleolithic sample, using only those remains that had not been buried. But we got similar results. The conclusion was inescapable: adult survivorship soared very late in human evolution.

BIOLOGY OR CULTURE?

NOW THAT LEE AND I had established that the number of potential grandparents surged at some point in the evolution of anatomically modern humans, we had another question on our hands:

NATURAL HISTORY MUSEUM, LONDON (*flint point and side scraper*); WALTER GEIERSPERGER *Corbis (Venus figurine*); GETTY IMAGES (*flute*); DIDIER DESCOUENS *Museum of Toulouse, France (burin)*

© 2015 Scientific American

What was it that brought about this change? There were two possibilities. Either longevity was one of the constellations of genetically controlled traits that biologically distinguished anatomically modern humans from their predecessors, or it did not come along with the emergence of modern anatomy and was instead the result of a later shift in behavior. Anatomically modern humans did not burst onto the evolutionary scene making the art and advanced weaponry that define Upper Paleolithic culture. They originated long before those Upper Paleolithic Europeans, more than 100,000 years ago, and for most of that time they and their anatomically archaic contemporaries the Neandertals used the same, simpler Middle Paleolithic technology. (Members of both groups appear to have dabbled in making art and sophisticated weapons before the Upper Paleolithic, but these traditions were ephemeral compared with the ubiquitous and enduring ones that characterize that later period.) Although our study indicated that a large increase in grandparents was unique to anatomically modern humans, it alone could not distinguish between the biological explanation and the cultural one, because the modern humans we looked at were both anatomically and behaviorally modern. Could we trace longevity back to earlier anatomically modern humans who were not yet behaviorally modern?

To address this question, Lee and I analyzed Middle Paleolithic humans from sites in western Asia dating to between about 110,000 and 40,000 years ago. Our sample included both Neandertals and modern humans, all associated with the same comparatively simple artifacts. This approach allowed us to compare the OY ratios of two biologically distinct groups (many scholars consider them to be separate species) who lived in the same region and had the same cultural complexity. We found that the Neandertals and modern humans from western Asia had statistically identical OY ratios, ruling out the possibility that a biological shift accounted for the increase in adult survivorship seen in Upper Paleolithic Europeans. Both western Asian groups had roughly even proportions of older and younger adults, putting their OY ratios between those of the Neandertals and early modern humans from Europe.

Compared with European Neandertals, a much larger proportion of western Asian Neandertals (and modern humans) lived to be grandparents. This is not unexpected—the more temperate environment of western Asia would have been far easier to survive in than the harsh ecological conditions of Ice Age Europe. Yet if the more temperate environment of western Asia accounts for the elevated adult survivorship seen in the Middle Paleolithic populations there, the longevity of Upper Paleolithic Europeans is even more impressive. Despite living in much harsher conditions, the Upper Paleolithic Europeans had an OY ratio more than double that of the Middle Paleolithic modern humans.

SENIOR MOMENTS

WE DO NOT KNOW EXACTLY what those Upper Paleolithic Europeans started doing culturally that allowed so many more of them to live to older age. But there can be no doubt that this increased adult survivorship itself had far-reaching effects. As Kristen Hawkes of the University of Utah, Hillard Kaplan of the University of New Mexico and others have shown in their studies of several modern-day hunter-gatherer groups, grandparents routinely contribute economic and social resources to their descendants, increasing both the number of offspring their children can have and the survivorship of their grandchildren. Grandparents also reinforce complex social connections—like my grandmother did in telling stories of ancestors that linked me to other relatives in my generation.

Elders transmit other kinds of cultural knowledge, too—from environmental (what kinds of plants are poisonous or where to find water during a drought, for example) to technological (how to weave a basket or knap a stone knife, perhaps). Multigenerational families have more members to hammer home important lessons. Thus, longevity presumably fostered the intergenerational accumulation and transfer of information that encouraged the formation of intricate kinship systems and other social networks.

Increases in longevity would also have translated into increases in population size by adding an age group that was not there in the past and that was still fertile. And large populations are major drivers of new behaviors. In 2009 Adam Powell, then at University College London, and his colleagues published a paper in *Science* showing that population density figures importantly in the maintenance of cultural complexity. They and many other researchers argue that larger populations promoted the development of extensive trade networks, complex systems of cooperation, and material expressions of individual and group identity (jewelry, body paint, and so on). Viewed in that light, the hallmark features of the Upper Paleolithic look as though they might well have been consequences of swelling population size.

Growing population size would have affected our forebears another way, too: by accelerating the pace of evolution. As John Hawks of the University of Wisconsin–Madison has emphasized, more people mean more mutations and opportunities for advantageous mutations to sweep through populations as their members reproduce. This trend may have had an even more striking effect on recent humans than on Upper Paleolithic ones, compounding the dramatic population growth that accompanied the domestication of plants 10,000 years ago.

The relation between adult survivorship and the emergence of sophisticated new cultural traditions was almost certainly a positive feedback process. Initially a by-product of some sort of cultural change, longevity became a prerequisite for the complex behaviors that signal modernity. These innovations in turn promoted the importance and survivorship of older adults, which led to the population expansions that had such profound cultural and genetic effects on our predecessors. Older and wiser, indeed. SA

Rachel Caspari is professor of anthropology at Central Michigan University. Her research focuses on Neandertals, the origin of modern humans and the evolution of longevity.

MORE TO EXPLORE

Older Age Becomes Common Late in Human Evolution. Rachel Caspari and Sang-Hee Lee in *Proceedings of the National Academy of Sciences USA*, Vol. 101, No. 30, pages 10,895–10,900; July 27, 2004.

Is Human Longevity a Consequence of Cultural Change or Modern Human Biology? Rachel Caspari and Sang-Hee Lee in *American Journal of Physical Anthropology*, Vol. 129, pages 512–517; April 2006.

The Process of Modern Human Origins: The Evolutionary and Demographic Changes Giving Rise to Modern Humans. Rachel Caspari and Milford H. Wolpoff in *The Origins of Modern Humans: Biology Reconsidered*. Edited by Fred H. Smith and James C. M. Ahern. Wiley-Blackwell, 2013.

© 2015 Scientific American

STRATEGIES

MEMORY IN OLD AGE: NOT A LOST CAUSE

Researchers have found ways to lessen age-related forgetfulness

By Hal Arkowitz and Scott O. Lilienfeld

When Mick Jagger first sang "What a drag it is getting old," he was 23 years old. Now at 71, he is still a veritable Jumpin' Jack Flash on stage. Jagger seems to have found the secret to staying physically fit in his advancing years, but getting old can be a drag on the psyche. Many older adults fear memory loss and worry they are headed down the road to dementia, such as Alzheimer's disease. Every time they forget their keys, leave a door unlocked or fail to remember a name, they are reminded of this nagging concern. In most cases, however, such annoying incidents are part of normal age-related memory loss, not a sign of impending dementia.

Although lots of older adults think such a decline is inevitable, there is good news for many of them. Researchers have developed an array of activities for exercising our minds and bodies that can help shore up memory in the normal aging brain.

MEMORY DIVIDED

Memory is not a single entity. The term encompasses several types of remembering, not all of which decline with age. For instance, older people still retain their vocabulary, along with general knowledge about the world (semantic memory). They can

Illustration by Sébastien Thibault

© 2015 Scientific American

also perform certain routine tasks, such as making an omelet or typing on a computer (procedural memory), about as well as they could when they were younger. People do become worse, however, at recalling recent events in their lives (episodic memory) or where they first learned a piece of information (source memory), managing the temporary storage of short-term information (working memory), and remembering to do things in the future (prospective memory).

Prospective memory, in particular, is a key target for memory strategies because forgetting upcoming tasks or appointments can cause considerable frustration or embarrassment. In 2002 psychologist Narinder Kapur of Southampton General Hospital in England and his colleagues reviewed studies on the effectiveness of various common techniques to bolster prospective memory. They found that external aids such as making lists or programming reminders into a cell phone could be helpful in reducing memory problems such as failing to pay bills or attend meetings.

TO REMEMBER TO BUY A BIRTHDAY GIFT FOR HIS WIFE, A MAN MIGHT CONSTRUCT THE ACRONYM "BIG" FOR "BUY GIFT."

Another successful strategy involves associating information to be recalled with an image, sentence, phrase or word. The more personally relevant the association is, the more likely it is to be remembered, an approach known as self-referential processing. For example, if we need to return a book to the library, we might imagine ourselves doing just that. Made-up acronyms also can be a huge help. In this strategy, a person forms a new word from the initial letters of what he or she wants to remember. To remember to buy a birthday gift for his wife, for example, a man might construct the acronym "BIG" for "Buy Gift."

In 2008 psychologists Elizabeth L. Glisky of the University of Arizona and Martha L. Glisky, then at Evergreen Hospital Medical Center in Seattle, described other useful methods for improving memory that involve visual or semantic elaboration. In one of these, a person conjures up images related to something he or she wants to retain. To remember the name "Peggy," you might imagine a pirate with a wooden (peg) leg. Such a tactic could be helpful as long as you do not end up calling her "Pegleggy."

A semantic approach entails tacking on words to what you wish to recall. For example, in a music appreciation class that one of us (Arkowitz) took in elementary school, the teacher asked the class to associate the main musical theme of the classical piece, the *Peer Gynt Suite,* with the following rather silly sentence: "Morning is dawning and Peer Gynt is yawning and music is written by Grieg." The tie-in with the phrase was designed to help the kids remember the name of the composer.

Although Glisky and Glisky found support for these visual and semantic techniques, among others, they cautioned that memory improvements in the laboratory do not necessarily translate to enhancements in daily life, because these benefits depend on people practicing and using the tactics regularly. This gap in efficacy may be widest for strategies that take considerable time and effort to learn. Also, improvements in one area of memory often do not generalize to others.

Studies have found some support for the validity of the saying "Use it or lose it." The more we use our memory—for example, reading, doing crossword puzzles and playing board games—the better it may be, probably because such activities involve considerable use of memory. Of course, those with better memories may also be more likely to exercise their minds in the first place, accounting for some (but probably not all) of the association between good memory and amount of cognitive stimulation.

FIT BODY, FIT MIND

IF JAGGER IS AS PHYSICALLY FIT AS HE LOOKS, his mind may be following suit. Some studies have found that higher levels of aerobic exercise are associated with better memory in older adults. Although many of these studies do not prove that aerobic exercise causes the memory improvements, some do suggest a causal connection. When psychologist Stanley Colcombe, then at the University of Illinois at Urbana-Champaign, and his colleagues reviewed 18 controlled studies addressing this association in 2003, they found evidence that aerobic exercise did indeed lead to better memory.

Sustained aerobic activity may not be the only way to keep your mind agile and your memory sharp. In a study published in 2011 neurologist Ruth Ruscheweyh, then at the University of Münster in Germany, and her colleagues assessed total physical activity in 62 older adults over six months. Their questionnaire included both formal exercise and daily routines such as walking to work, climbing stairs and gardening. The researchers linked reported increases in overall activity, no matter its type, with improvements in episodic memory at the end of six months. The greater the rise in activity levels, the bigger the memory boost. Thus, keeping physically active through regular workouts along with everyday errands and tasks may be the best recipe for reinvigorating your powers of recollection. [For more on the connection between physical and mental fitness in old age, see "Fit Body, Fit Mind?" by Christopher Hertzog, Arthur F. Kramer, Robert S. Wilson and Ulman Lindenberger, on page 40.]

The research suggests that many memory techniques as well as a physically and mentally energetic lifestyle can improve memory in older adults. We still have a long way to go before we have highly effective methods, but given the vigor of this field, we can expect great progress in the near future. SA

Hal Arkowitz and **Scott O. Lilienfeld** serve on the board of advisers for *Scientific American Mind.* Arkowitz is an associate professor of psychology at the University of Arizona, and Lilienfeld is a psychology professor at Emory University.

MORE TO EXPLORE

Memory Rehabilitation in Older Adults. Elizabeth L. Glisky and Martha L. Glisky in *Cognitive Neurorehabilitation: Evidence and Applications.* Second edition. Edited by Donald Tuss, Gordon Winocur and Ian Robertson. Cambridge University Press, 2008.

Train Your Brain: How to Maximize Memory Ability in Older Adults. Robert Winningham. Baywood Publishing Company, 2009.

Physical Activity and Memory Functions: An Interventional Study. R. Ruscheweyh, C. Willemer, K. Krüger, T. Duning, T. Warnecke, J. Sommer, K. Völker, H. V. Ho, F. Mooren, S. Knecht and A. Flöel in *Neurobiology of Aging,* Vol. 32, No. 7, pages 1304–1319; 2011.

scientificamerican.com/magazine/sa

© 2015 Scientific American

NEUROSCIENCE

SLOWING AGE-BASED MEMORY LOSS

The elderly may be able to improve recall of words and faces by associating them with locations in a "memory palace"

By Shelly Fan

One of the tragedies of aging is the slow but steady decline in memory. Phone numbers slipping your mind? Forgetting crucial items on your grocery list? Opening the door but can't remember why? Over half of adults aged 64 years or older report memory complaints. For many of us, senile moments are the result of normal changes in brain structure and function, instead of a sign of dementia, and will inevitably haunt us all.

Fortunately, scientists are devising interventions to help keep the elderly mind sharp. One popular approach—borrowed from the training of memory experts—is to teach the elderly mnemonics, or little tricks that help to encode and recall new information using rhythm, imagery or spatial navigation.

By far the most widely used mnemonic device is the method of loci (MoL), a technique devised in ancient Greece. It involves picturing highly familiar routes through a building (your childhood home) or a town (your way to work). Walk down the route and imagine placing to-be-remembered items at attention-grabbing spots along the way; the more surreal or bizarre you make these images, the better they can help you remember. To recall these stored items, simply retrace your steps. Like fishing lines, the loci are hooked to the memory and help you pull them to the surface. Though generally used to remember objects, numbers or names, the MoL has also been used in people with depression to successfully store bits and pieces of happy autobiographical memories that they can easily retrieve in times of stress.

Yet with age, the brain gradually loses the flexibility to change in response to training. Nevertheless, many studies show that MoL successfully slows memory decline in the normal aging population, but why this happens is a complete mystery. That is, until recently.

THICKENING OF THE BRAIN

In 2010 a Norwegian team set out to look for the most obvious sign of MoL-induced neuroplasticity: macrostructural changes in the brain. Expert instructors led 23 volunteers with an average age of 61 through an intensive eight-week-long program. By the end of training, these volunteers were able to use MoL to remember three lists of 30 words in sequential order in no more than 10 minutes. The control group—matched in age, sex and education—went about their daily lives as usual for the same duration. During the final test, researchers challenged both groups with a tough task: they first flashed a list of 15 unrelated words, each for only a second, and asked the volunteers to remember the words in order. Researchers then showed them a list of 30 words—15 previously presented and 15 new—and asked both groups to not only pick out the matching words but also to identify their position in the first list. Because the second task involves spatial recognition, researchers reasoned that it should particularly benefit from MoL training.

As expected, MoL-trained volunteers correctly named the position of six more words, on average, than did the volunteers who were not trained, although both groups recognized a similar number of matching words. Structural MRI images taken before and after training identified a surprisingly large morphological change in the MoL-trained volunteers. These individuals showed significant thickening of the right fusiform cortex and the right orbitofrontal cortex, areas particularly involved in encoding abstract visual memory. The degree of thickening correlated with memory improvement: the larger the change, the better the performance.

The control group showed a trend toward thinning of their cortices, perhaps as a result of cortical atrophy in normal aging. A later study from the same group showed that learning MoL also preserves the structural integrity of white matter—the myelinated axons of nerve cells that form communication highways between brain regions.

This initial sleuthing shows that the elderly brain is still remarkably adaptable as it learns to process verbal information using spatial imagery. While intriguing, these studies only just scratched the surface: the volunteers were self-selected through answering a newspaper ad, and the small sample size cautions against generalization. Furthermore, these changes may reflect a general increase in cognitive load rather than the use of MoL per se. Still, compared with other mnemonics, the benefits of MoL often persist after initial training even without subsequent practice, strongly suggesting that structural changes underlie the method's long-term benefits.

© 2015 Scientific American

REWIRING THE BRAIN

STRUCTURAL CHANGES do not necessarily lead to changes in function. To directly assess whether the brain operates differently following MoL training, two groups of researchers decided to look at brain-activity patterns instead. In a 2003 study, Swedish scientists recruited volunteers in their twenties and sixties and used positron-emission tomography (PET) scans to follow changes in their brain activity as they adopted MoL to remember a list of random words. Several mentally grueling sessions later, all of the young volunteers—but only half of the elderly—remembered roughly four more words than they had in their initial test, with the younger crowd performing much better on average.

Those who improved showed increased activity in the occipitoparietal cortex and left retroplenial cortex during encoding. These brain regions are associated with spatial mental visualization and navigation. A similar pattern of activation was previously found in world-class memory champions as they spontaneously used MoL for memory tasks. This suggests that the observed changes were in fact a result of adopting the mnemonic, and that despite old age, the brain is still capable of a qualitative shift in the way it encodes new memories. A later study using functional MRI confirmed these results and further implicated the fusiform and lingual gyri in memory encoding.

What about the half of elderly participants who did not improve? One clue was their complete lack of activation of MoL-associated brain regions during testing, prompting researchers to wonder whether these volunteers actually used MoL during the experiment. As it turned out, they did not! A subsequent informal chat revealed that many older participants found it difficult to associate loci with words under the experiment's tight time constraints, felt frustrated and gave up. This seems to be a general response: a recent study involving more than 700 mnemonic-trained older adults found that only 25 percent made an effort to use MoL after initial learning in a series of follow-up sessions spanning five years.

Though a promising technique for many, MoL is particularly difficult for the elderly, who are less able to generate and rely on a mental map of distinctive landmarks. Is there any way to lower the barrier of entry for learning MoL?

MODERNIZING THE MNEMONIC

IN EARLY 2012 a team of Canadian researchers gave the ancient MoL mnemonic a 21st-century facelift. Inspired by the first-person shooter game Half-life 2, the team constructed several detailed virtual-reality environments to serve as loci, rather than letting MoL learners generate their own. This technique deviated from the long-standing rule that the loci need to be of personal significance for the method to work.

But it paid off. Researchers allowed 142 undergraduate volunteers only five minutes to explore the virtual environment before asking them to memorize 110 unrelated words. Before the task began, the researchers taught two thirds of the volunteers how to use MoL and asked some of them to pick a familiar environment for their loci; the rest of this group was told to use the virtual environment they had just navigated. The other third of the volunteers did not receive any specific instructions on memory techniques.

Both MoL groups outperformed the controls. They were 10 to 16 percent more accurate in their recall, and students who used the virtual environment performed just as well as those told to generate their own landmarks. The interesting bit is that in both groups, participants reported that they sometimes used memory methods that they were more familiar with during the task. Compared with participants in the standard MoL group, however, those using the virtual environment took to the mnemonic more readily, suggesting that this approach was easier to adopt.

Extrapolating data from young adults to the aging population warrants caution, but researchers are optimistic. By using software that creates many diverse environments, the elderly may be able to tailor the richness and theme of each space to both their learning ability and to what they wish to remember. A young scientist from Belgium is dreaming big: in a 2013 TEDx talk, Kasper Bormans described using virtual-reality replicas of the homes of Alzheimer's disease patients to help them "store" the memory of their loved one's faces using MoL. By combining the mnemonic with training in other cognitive domains—logic and reasoning, organization and attention—as well as antidementia medication where needed, researchers hope to slow (if not halt) the memory loss that haunts our twilight years. SA

KEN HERMANN *Getty Images*

Mentally "placing" surreal images along a familiar route can aid memory. For example, visualizing an astronaut at a specific spot might help you remember the name "Armstrong."

Shelly Fan is a Ph.D. candidate in neuroscience at the University of British Columbia, where she studies neurodegeneration. She is a freelance science writer, editor at ScienceSeeker.org and a Banff Science Communications Program alumna. She mulls over neuroscience, microbiomes and nutrition at Neurorexia (www.neurorexia.com).

MORE TO EXPLORE

Neural Correlates of Training-Related Memory Improvement in Adulthood and Aging. Lars Nyberg, Johan Sandblom, Sari Jones, Anna Stigsdotter Neely, Karl Magnus Petersson, Martin Ingvar and Lars Bäckman in *Proceedings of the National Academy of Sciences USA*, Vol. 100, No. 23, pages 13,728–13,733; November 11, 2003.

Effects of Memory Training on Cortical Thickness in the Elderly. Andreas Engvig, Anders M. Fjell, Lars T. Westlye, Torgeir Moberget, Øyvind Sundseth, Vivi Agnete Larsen and Kristine B. Walhovd in *NeuroImage*, Vol. 52, No. 4, pages 1667–1676; October 1, 2010.

Building a Memory Palace in Minutes: Equivalent Memory Performance Using Virtual versus Conventional Environments with the Method of Loci. Eric L. G. Legge, Christopher R. Madan, Enoch T. Ng and Jeremy B. Caplan in *Acta Psychologica* Vol. 141, No. 3, pages 380–390; November 2012.

Do Older Adults Use the Method of Loci? Results from the ACTIVE Study. Alden L. Gross, Jason Brandt, Karen Bandeen-Roche, Michelle C. Carlson, Elizabeth A. Stuart, Michael Marsiske and George W. Rebok in *Experimental Aging Research*, Vol. 40, No. 2, pages 140–163; March 2014.

scientificamerican.com/magazine/sa

© 2015 Scientific American

PHARMACOLOGY

IT'S NOT DEMENTIA, IT'S YOUR HEART MEDICATION

Why cholesterol drugs might affect memory

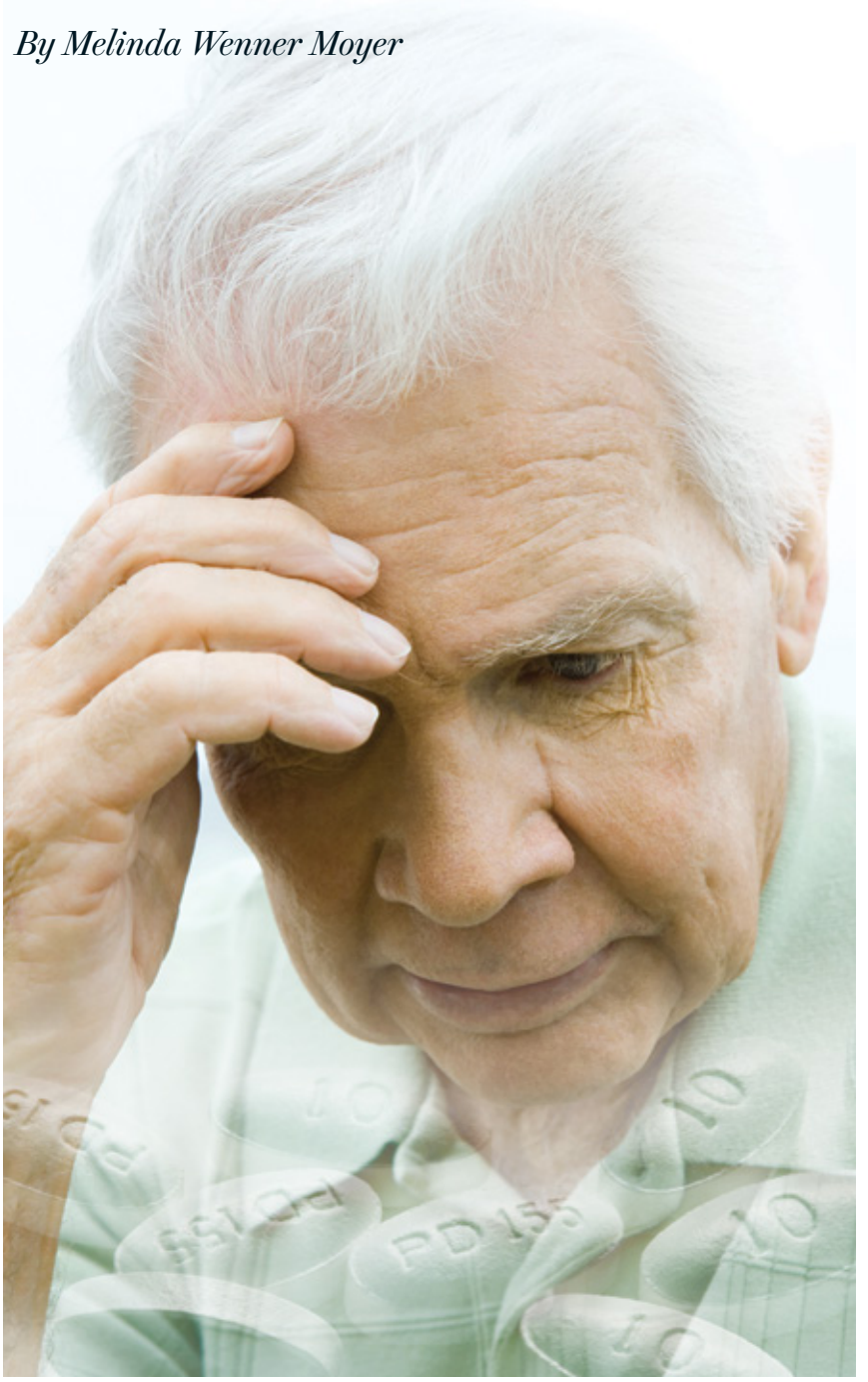
By Melinda Wenner Moyer

ONE DAY IN 1999 FORMER NASA astronaut Duane Graveline, then 68 years old, returned home from his morning walk in Merritt Island, Fla., and could not remember where he was. His wife stepped outside, and he greeted her as a stranger. When Graveline's memory returned some six hours later in the hospital, he racked his brain to figure out what might have caused this terrifying bout of amnesia. Only one thing came readily to mind: he had recently started taking the statin drug Lipitor.

Cholesterol-lowering statins such as Lipitor, Crestor and Zocor are the most widely prescribed medications in the world, and they are credited with saving the lives of many heart disease patients. But recently a small number of users have voiced concerns that the drugs elicit unexpected cognitive side effects, such as memory loss, fuzzy thinking and learning difficulties. Hundreds of people have registered complaints with MedWatch, the U.S. Food and Drug Administration's adverse drug reaction database, but few studies have been done and the results are inconclusive. Nevertheless, many experts are starting to believe that a small percentage of the population is at risk, and they are calling for increased public awareness of the possible cognitive side effects of statins—symptoms that may be misdiagnosed as dementia in the aging patients who take them. In 2012, the FDA expanded the warning labels on all statins to include "notable, but ill-defined memory loss or impairment."

FAT AND THE BRAIN

IT IS NOT CRAZY to connect cholesterol-modifying drugs with cognition; after all, one



Some people may have a genetic predisposition to suffer cognitive side effects, such as fuzzy thinking, when they are taking cholesterol-lowering drugs.

CORBIS (man); CHRIS GALLAGHER Photo Researchers, Inc. (Lipitor pills)

© 2015 Scientific American

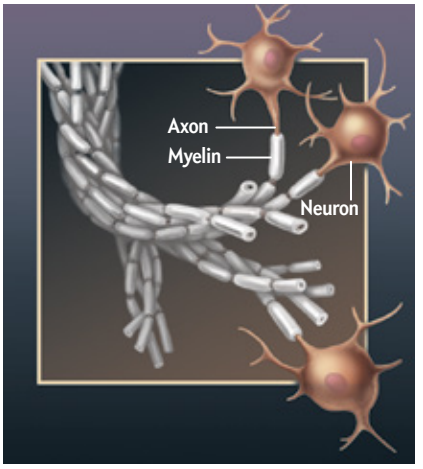
quarter of the body's cholesterol is found in the brain. Cholesterol is a waxy substance that, among other things, provides structure to cell membranes. High levels of cholesterol in the blood create a risk for heart disease, because the molecules that transport cholesterol can damage arteries and cause blockages. In the brain, however, cholesterol plays a crucial role in the formation of neuronal connections—the vital links that underlie memory and learning. Quick thinking and rapid reaction times depend on cholesterol, too, because the waxy molecules are the building blocks of the sheaths that insulate neurons and speed up electrical transmissions [*see illustration at right*]. "We can't understand how a drug that affects such an important pathway would not have adverse reactions," says Ralph Edwards, former director of the World Health Organization's drug-monitoring center in Uppsala, Sweden.

Two small trials published in 2000 and 2004 by Matthew Muldoon, a clinical pharmacologist at the University of Pittsburgh, seem to suggest a link between statins and cognitive problems. The first, which enrolled 209 high-cholesterol subjects, reported that participants taking placebo pills improved more on repeated tests of attention and reaction time taken over the course of six months—presumably getting better because of practice, as people typically do. Subjects who were on statins, however, did not show the normal improvement. The second trial reported similar findings. And a study published in 2003 in *Reviews of Therapeutics* noted that among 60 statin users who had reported memory problems to MedWatch, more than half said their symptoms improved when they stopped taking the drugs.

But other studies have found no significant link between statins and memory problems. The late Larry Sparks, when he was director of the Laboratory for Neurodegenerative Research at the Sun Health Research Institute in Sun City, Ariz., went so far as to say that "you've got a better chance of buying a winning lottery ticket, walking outside and getting hit by lightning and dying" than you do of suffering a cognitive side effect from statins.

VULNERABLE GENES?

MANY EXPERTS AGREE that for most people the risk is quite low, but they are beginning to believe the effects are real. "A subset of the population is vulnerable," argues Joe Graedon, co-founder of the consumer advocacy Web site the People's Pharmacy, which has collected hundreds of reports of cognitive-related statin side effects in the past decade. Some researchers believe these people have a genetic profile that puts them at risk.



Statins may prevent the body from making cholesterol-based myelin, which insulates axons and speeds neuron communication.

Beatrice A. Golomb, an associate professor of medicine at the University of California, San Diego, suggests that one at-risk group may be individuals with defects in their mitochondria, the structures within cells that make energy. Statins prevent the body from making an antioxidant that neutralizes the damaging free radicals created by mitochondrial activity. If brain cells—which consume lots of energy—already have mitochondrial problems, then statin therapy could tip the scale and cause noticeable symptoms, such as trouble learning.

Golomb's theory is supported by a study published in 2006 by geneticist Georgirene Vladutiu of the University at Buffalo. Vladutiu reported that statin users who experience muscle pain and weakness as a side effect are more likely than other users to have preexisting genetic defects related to cellular energy production. And as with brain cells, muscle cells are high energy users.

DIFFERENT FORMULATIONS

INTERESTINGLY, some studies suggest that statins might improve memory in certain people by lowering the risk of dementia. This benefit could occur because cholesterol is involved in the production of the protein clusters that are the hallmark of neurodegenerative diseases such as Alzheimer's and Parkinson's. But even if statins are neurologically protective for some, they may be problematic for others, given that the opposing effects probably arise through different biochemical pathways.

Because statins differ in their formulations and can affect so many processes, and because users have different genetic predispositions, simply switching drugs might help people who are experiencing warning signs such as forgetting names. A 2009 *Pharmacotherapy* study published by Golomb and Marcella A. Evans, a graduate student at the University of California, Irvine, analyzed the characteristics of 171 statin users who reported cognitive side effects. Their findings suggest that people who take the more potent statins—Crestor and Lipitor—are at an increased risk compared with those who take weaker statins.

Graveline, for one, is certain that Lipitor was to blame for his 1999 amnesia incident. Although he immediately stopped taking the drug, his doctor—who was skeptical—convinced him a year later to give it another shot. Sure enough, after another eight weeks of treatment, he suffered a second episode. Graveline has been statin-free ever since, instead following a healthy diet to keep his cholesterol low, and he says he has never felt better. But he also knows that for many, the benefits that statins provide will overshadow their risks. "I'm not asking for statins to be taken off the market," he says. "I'm just asking for physicians to be aware of their side effects." SA

Melinda Wenner Moyer is an award-winning science writer based in Cold Spring, N.Y.

MORE TO EXPLORE

Statins and Cognition: What Can We Learn from Existing Randomized Trials? G. L. Xiong, A. Benson and P. M. Doraiswamy in *CNS Spectrums*, Vol. 10, No. 11, pages 867–874; November 2005.

Statin-Associated Adverse Cognitive Effects: Survey Results from 171 Patients. Marcella A. Evans and Beatrice A. Golomb in *Pharmacotherapy*, Vol. 29, No. 7, pages 800–811; July 2009.

scientificamerican.com/magazine/sa

JEN CHRISTIANSEN

© 2015 Scientific American

PHYSIOLOGY

FIT BODY, FIT MIND?

How can you stay sharp into old age? It is not just a matter of winning the genetic lottery. What you do can make a difference

By Christopher Hertzog, Arthur F. Kramer, Robert S. Wilson and Ulman Lindenberger

IN BRIEF

We are used to thinking of intelligence as largely a matter of genetic inheritance, but that is not the whole picture. What we do affects our mental well-being: staying physically and mentally active helps us stay sharp as we age.

Nevertheless, our personal efforts to bolster cognitive enhancement cannot forestall all declines in our cognitive performance.

What is especially surprising is the powerful link between physical activity and mental acuity. Staying fit helps us keep cognition more robust as well. Older adults who participate in aerobic exercise outperform their peers who do not.

NOAH CLAYTON *Getty Images*

© 2015 Scientific American

© 2015 Scientific American

AS EVERYBODY KNOWS, IF YOU DO NOT WORK OUT, YOUR MUSCLES GET FLACCID. WHAT most people don't realize, however, is that your brain also stays in better shape when you exercise. And not just challenging your noggin by, for example, learning a new language, doing difficult crosswords or taking on other intellectually stimulating tasks. As researchers are finding, *physical* exercise is critical to vigorous mental health, too.

Surprised? Although the idea of exercising cognitive machinery by performing mentally demanding activities—popularly termed the "use it or lose it" hypothesis—is better known, a review of dozens of studies shows that maintaining a mental edge requires more than that. Other things you do—including participating in activities that make you think, getting regular exercise, staying socially engaged and even having a positive attitude—have a meaningful influence on how effective your cognitive functioning will be in old age.

Further, the older brain is more plastic than is commonly known. At one time, the accepted stereotype was that "old dogs can't learn new tricks." Science has proved that this dictum must be discarded. Although older adults generally learn new pursuits more slowly than younger people do and cannot reach the peaks of expertise in a given field that they might have achieved if they had

K-P WOLF Getty Images

Stimulating challenges such as puzzles help us keep our edge.

© 2015 Scientific American

started in their youth, they nonetheless can improve their cognitive performance through effort—forestalling some of the declines in cognition that come with advancing age. As John Adams, one of the founding fathers and the second U.S. president, put it: "Old minds are like old horses; you must exercise them if you wish to keep them in working order."

The news comes at a propitious time. The proportion of older adults in the U.S. and in other industrial nations continues to grow: in 1900, 4.1 percent of U.S. citizens were older than 65, but by 2000 that amount had jumped to 12.6 percent; by 2030, 20 percent of us will be in that category. From a societal point of view, prolonging independent functioning is both a desirable goal in itself and a way of deferring costs of long-term care. For individuals, maintaining optimal cognitive functioning is worthwhile simply because it promises to enhance quality of life through the years.

MENTAL TRAINING

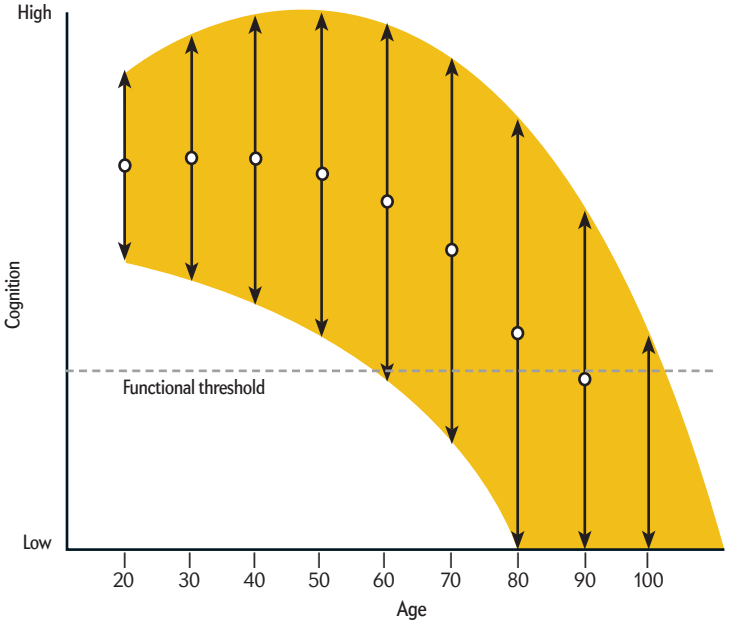
HOW TO KEEP MINDS keen over an entire life span is a question philosophers have mulled since the earliest writings on record. As Roman orator Cicero put it: "It is exercise alone that supports the spirits, and keeps the mind in vigor." Modern research in this field began in the 1970s and 1980s, with studies that demonstrated that healthy older adults can improve performance to a greater extent than had been previously assumed. The earlier research did not fully address certain questions, such as how long adults could retain the new skills they had acquired through training, whether those specifically developed skills would also positively influence other areas of cognition needed in everyday life, and whether the studies done with small numbers of subjects would be broadly applicable.

Cognitive training can lead to substantial benefits for older adults on the tasks trained, and some of these benefits are maintained over time and may transfer to other tasks. Toward the end of the 20th century the National Institute on Aging funded a consortium of researchers to conduct a large-scale training study in a sample of older Americans. In 2002 psychologist Karlene Ball of the University of Alabama at Birmingham and her colleagues published initial results on more than 2,500 individuals old-

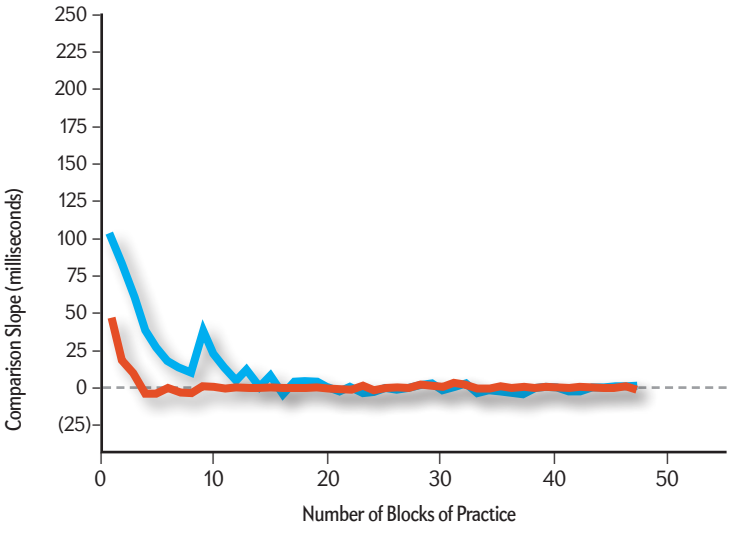
FINDINGS

Capabilities over Time

An individual's cognitive function can vary from maturity into old age. Although good habits can promote sound thinking within a given range (*top graph*), we cannot completely halt the effects of aging (*bottom graph*).



Everyone experiences cognitive decline over a lifetime, but exercising the mind and body can help individuals stay above the middle (*white dots*) of the cognitive range (*shaded area*) and remain functional even beyond age 90.



In one study of practice benefits, older adults (mean age 72, *blue*) were slower than younger adults (mean age 21, *red*) to search memory (comparison slope, *vertical axis*) to verify whether a word was one of a set they had committed to memory a short time earlier. But with enough practice, they could speedily identify target words without needing to search for them, producing zero slopes such as those produced by younger people.

SECRETS OF STAYING YOUNG

SCIENTIFIC AMERICAN MIND; SOURCE FOR TOP GRAPH: "ENRICHMENT EFFECTS ON ADULT COGNITIVE DEVELOPMENT: CAN THE FUNCTIONAL CAPACITY OF OLDER ADULTS BE PRESERVED AND ENHANCED?" BY C. HERTZOG ET AL., IN *PSYCHOLOGICAL SCIENCE IN THE PUBLIC INTEREST*, VOL. 9, NO. 1; OCTOBER 2008. © 2009 ASSOCIATION FOR PSYCHOLOGICAL SCIENCE; SOURCE FOR BOTTOM GRAPH: "AGING AND INDIVIDUAL DIFFERENCES IN THE DEVELOPMENT OF SKILLED MEMORY SEARCH PERFORMANCE," BY C. HERTZOG ET AL., IN *PSYCHOLOGY AND AGING*, VOL. 11, NO. 3; 1996

© 2015 Scientific American

er than 65 who had received about 10 sessions of cognitive training. Participants were randomly assigned either to a cognitive-process training group to learn how to excel in one of three areas—memory, reasoning or visual search—or to a control group of subjects who did not receive training. At a follow-up two years later, the team randomly selected a set of the initial participants for booster training prior to evaluation. The results showed strong training-effect sizes in each group as compared with controls. In retests five years later, measurable training benefits were still present.

More impressive, however, are recent training studies that focus on what psychologists call working memory and executive functions—how a person plans a strategic approach to a task, controls what is attended to, and how he or she manages the mind in the process. Psychologist Chandramallika Basak, then at the University of Illinois, and her colleagues showed that training in a real-time strategy video game that demands planning and executive control not only improved gaming performance but also enhanced performance on other tasks measuring aspects of executive control.

Some studies have also increased the amount of practice provided. For instance, Florian Schmiedek and one of us (Lindenberger) of the Max Planck Institute for Human Development in Berlin and Martin Lövdén of the Karolinska Institute in Stockholm asked 101 younger and 103 older adults to practice 12 different tasks for 100 days. Each of the tasks belonged to one of three different sets of cognitive skills—working memory, episodic memory and perceptual speed. Both younger and older adults showed general improvements in working memory. Younger adults also broadly improved in memory and reasoning and maintained their gains in reasoning over a period of two years.

AFTER SIX TO EIGHT YEARS, THEY ASSESSED THE WOMEN'S LEVEL OF COGNITIVE FUNCTION. THE MOST ACTIVE HAD A 30 PERCENT LOWER RISK OF DECLINE.

You do not have to have specialized training, however, to achieve cognitive gains or ward off cognitive decline. Everyday activities such as reading can help. We reviewed evidence on activity-related cognitive enrichment in more than a dozen studies. In 2003 one of us (Wilson) and his colleagues at Rush University Medical Center in Chicago recruited more than 4,000 elderly people from a geographically defined community and rated their frequency of participation in seven cognitive activities (for instance, reading magazines). At three-year intervals for a mean of nearly six years, participants completed an in-home interview that included brief tests of cognitive function. More frequent cognitive activity at the outset was associated with reduced rate of cognitive decline over time. But not all studies of staying cognitively active have found such benefits.

GETTING PHYSICAL

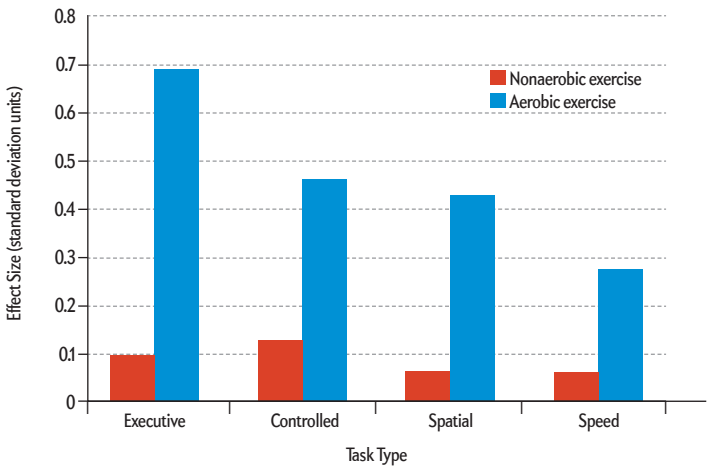
OVER THE PAST DECADES several studies have underscored the link between physical activity and cognition. For instance, in a study published in 2001 neuropsychiatrist Kristine Yaffe of the University of California, San Francisco, and her colleagues recruited 5,925 women older than 65 at four different medical centers across the U.S. The participants were all free of any physical disability that would limit their ability to walk or pursue other physical activities. The volunteers were also screened to ensure that they did not have a cognitive impairment. The researchers then assessed their physical activity by asking the women how many city blocks they walked and how many flights of stairs they climbed daily and gave them a questionnaire to fill out about their levels of participation in 33 different physical activities.

After six to eight years, the researchers assessed the women's level of cognitive function. The most active women had a 30 percent lower risk of cognitive decline. Interestingly, walking distance was related to cognition, but walking speed was not. It seems that even moderate levels of physical activity can serve to limit declines in cognition.

COMPARISON

The Power of Walking

Older adults who participated in aerobic exercise (walking) outperformed those in programs for stretching and toning (controls) in cognitive task areas: executive (related to planning and multitasking), controlled (effortful processes in response to novel situations), spatial (dealing with spatial information in perception or memory) and speed.



SOURCE: "FITNESS EFFECTS ON THE COGNITIVE FUNCTION OF OLDER ADULTS: A META-ANALYTIC STUDY" BY STANLEY J. COLCOMBE AND ARTHUR F. KRAMER, IN *PSYCHOLOGICAL SCIENCE*, VOL 14, NO. 2, MARCH 2003

© 2015 Scientific American

Physical activity bolsters memory and thwarts dementia.

CIRCLESTOCK *Corbis*

Moderate movement is good, but toning your circulatory system with aerobic exercise may be the real key to brain fitness. In a 1995 study of 1,192 healthy 70- to 79-year-olds, cognitive neuroscientist Marilyn Albert of Johns Hopkins University and her colleagues measured cognition with a battery of tasks that took approximately 30 minutes to complete and included tests of language, verbal memory, nonverbal memory, conceptualization and visuospatial ability. They found that the best predictors of cognitive change over a two-year period included strenuous activity and peak pulmonary expiratory flow rate.

In an investigation published in 2004 epidemiologist Jennifer Weuve, then at Harvard University, and her colleagues also examined the relation between physical activity and cognitive change over a two-year period in 16,466 nurses who were older than 70. Participants logged how much time they spent per week in a variety of physical activities (running, jogging, walking, hiking, racket sports, swimming, bicycling, aerobic dance) over the past year and provided self-reports of walking pace in minutes per mile. Weuve's group observed a significant relation between energy expended in physical activities and cognition, across a large set of cognitive measures.

The research that we have described thus far has examined mental performance over relatively short periods—just several years. A few studies have begun to look at what happens over longer timescales. In 2005 Suvi Rovio, now at the University of Turku in Finland, and her colleagues examined the relation between physical activity at middle age and risk of dementia an average of 21 years later, when the cohort was between 65 and 79 years of age. Subjects indicated how often they participated in leisure-time physical activities that lasted at least 20 to 30 minutes and caused breathlessness and sweating. Conducting such activity at midlife at least twice a week was associated with a reduced risk of dementia in later life. Indeed, participants in the more active group had 52 percent lower odds of having dementia than the more sedentary group did.

In 2010 Kirk Erickson and his colleagues at the University of Pittsburgh extended previous research examining the relation between physical activity, cognition and dementia by assessing self-reported physical activity alongside measures of regional brain volume. They reported an association between walking and retention of brain volume, which in turn predicted a reduced risk of dementia in 299 older adults over a period of 13

© 2015 Scientific American

Socializing—and even a positive attitude—helps your brain stay healthier.

years. Interestingly, it is not just aerobic forms of physical activity (such as walking, jogging, swimming and bicycling) that have been associated with improvements in cognition. Teresa Liu-Ambrose, a professor of physical therapy at the University of British Columbia, reported in 2010 that resistance exercise, over a one-year period, improved aspects of executive control in older women.

See the *Psychological Science in the Public Interest* article "Enrichment Effects on Adult Cognitive Development: Can the Functional Capacity of Older Adults Be Preserved and Enhanced?" on which this story for *Scientific American* was originally based, at the Association for Psychological Science's Web site: www.psychologicalscience.org

MIND-BODY CONNECTION

IT MAKES SENSE that training or participation in mentally stimulating activities would help cognition, but it is perhaps less immediately obvious why physical activity would have such an effect. Consider the increasingly well-documented link between physical activity and disease. A plethora of studies have examined the health benefits of exercise and a nonsedentary lifestyle for prevention of disease. For example, we now know that physical activity reduces the risk of cardiovascular-related death, type 2 diabetes, colon and breast cancer, and osteoporosis. On the other hand, cardiovascular disease, diabetes and cancer have been associated with compromised cognition. Therefore, you might expect that increased physical activity and exercise would maintain cognition by reducing risk of diseases associated with cognitive decline.

In a study published in 2006 psychologist Stanley J. Colcombe, then at the University of Illinois, and his colleagues examined the influence of fitness training on potential changes in brain structure. The six-month trial included 59 healthy but sedentary community-dwelling volunteers, age 60 to 79. Brain scans after fitness training showed that even relatively short exercise interventions can begin to restore some of the losses in brain volume associated with normal aging. In 2011 Erickson and his colleagues reported on work done at the University of Illinois, which showed that one year of walking, an hour a day for three days a week, increased the volume of the hippocampus in older adults. The hippocampus supports important aspects of memory such as associating an individual's face with her name and discussions that you might have had with her.

Supporting these findings, a large body of nonhuman animal research has demonstrated a number of changes in brain structure and function after animals are exposed to enriched, or complex, environments. Enriched environments usually include running wheels, a multitude of toys and objects to climb that are changed frequently, and animal companions. Exposure to such environments yields several physiological benefits. First, it increases the formation of new dendrite branches and synapses—the areas of neural cells that receive and send communication signals. It also increases the number of glial

JUPITERIMAGES

© 2015 Scientific American

cells, which support the health of neurons, and expands the brain's oxygen-supplying capillary network. Enriched environments foster the development of new neurons and create a cascade of molecular and neurochemical changes, such as an increase in neurotrophins—molecules that protect and grow the brain. Finally, physical activity in animals results in improvements in learning and memory.

Doing puzzles and push-ups are helpful for some—but other factors also boost mental fitness. For one, getting involved in social groups both improves cognition in general and seems to help thwart the arrival of dementia. The traditional focus of this research has been on relatively objective measures of social isolation versus connectedness, including the extent to which a person participates in activities that prominently involve social interaction (such as doing volunteer work), the number of friends and relatives an individual contacts regularly (in other words, the size of a person's social network), and marital status. Findings about the positive aspects of attitudes and beliefs on adult cognition are spottier. In large part, positive beliefs and attitudes may have important indirect effects on cognitive enrichment because of their influence on the kinds of behaviors (for instance, exercise and mentally stimulating activities) that are known to be associated with cognitive enrichment.

More generally, individuals who are optimistic, agreeable, open to new experiences, conscientious, positively motivated and goal-directed are more likely to undergo successful aging, to take advantage of opportunities, to cope effectively with life circumstances, to effectively regulate emotional reactions to events, and to maintain a sense of well-being and life satisfaction in the face of challenge.

And just as maintaining some activity patterns in old age may reduce risk of cognitive decline, the persistence of other patterns of behavior may increase the risk. Chronic psychological distress—resulting from depression, anxiety, and negative emotions such as anger and shame—is associated with a variety of negative outcomes in adulthood, including cognitive decline. The tendency to experience psychological distress is often called neuroticism. Studies have consistently found a higher level of neuroticism to be linked to an increased incidence of Alzheimer's disease and mild cognitive impairment in old age.

ENRICHING COGNITION

CLEARLY, THERE IS NO MAGIC PILL that inoculates the individual against cognitive decline in old age. Thus, public policy should follow a health prevention model. Policy leaders might promote intellectual activities that are inherently meaningful for older adults, perhaps as embedded in larger social contexts (for example, the Elderhostel movement or adult continuing education). A critical issue for future research will be to understand how an engaged way of life can be promoted and implemented in midlife, during the working years. Given inevitable conflicts between work demands and time available for other roles (parenting, for one) and activities, it would be useful to know whether work-related activity programs (such as availability and use of physical exercise facilities at or near the workplace) could help foster an enriching lifestyle.

POSITIVE ATTITUDES MAY HAVE IMPORTANT EFFECTS ON COGNITIVE ENRICHMENT BECAUSE OF THEIR INFLUENCE ON HEALTHY BEHAVIORS.

At the same time, the public must be aware that there is still much that is not known about cognitive fitness in old age, as well as some controversy about the magnitude and durability of mental exercise outcomes. People are marketing computer games and other means of exercising the mind, often making strong claims about the effectiveness of expensive products that have not been backed by actual scientific studies. Consumers should look for evidence demonstrating the benefits of such products—particularly with regard to everyday activities such as driving, memory for daily activities and better financial decision making.

The next decades offer much promise for expanding our knowledge about aging and cognition. We may soon discover whether the limits on successful cognitive functioning in old age that were once seen as insurmountable can ultimately be viewed as pessimistic assumptions that focused on observable age-related decline rather than the potential for maximizing human performance through cognitive enrichment. Just as advances in medical science may lead to increased longevity through vehicles such as effective treatments for dementia-causing illnesses, advances in psychological science can make important contributions to improving the quality of life of long-living older adults, in part by empirically demonstrating that attitudes and behaviors can promote cognitive functioning in old age and, more generally, by showing how behavioral interventions can help us all age successfully. SA

Christopher Hertzog is professor of psychology at the Georgia Institute of Technology. **Arthur F. Kramer** is professor of psychology and neuroscience and director of the Beckman Institute for Advanced Science and Technology at the University of Illinois. **Robert S. Wilson** is professor of behavioral and neurological sciences at Rush University Medical Center in Chicago. **Ulman Lindenberger** is director of the Center for Lifespan Psychology at the Max Planck Institute for Human Development in Berlin.

MORE TO EXPLORE

Relation of Cognitive Activity to Risk of Developing Alzheimer's Disease. R. S. Wilson, P. A. Scherr, J. A. Schneider, Y. Tang and D. A. Bennett in *Neurology,* Vol. 69, No. 20, pages 1911–1920; November 13, 2007.

The Neurogenic Reserve Hypothesis: What Is Adult Hippocampal Neurogenesis Good For? G. Kempermann in *Trends in Neuroscience,* Vol. 31, No. 4, pages 163–169; April 2008.

Hundred Days of Cognitive Training Enhance Broad Cognitive Abilities in Adulthood: Findings from the COGITO Study. F. Schmiedek, M. Lövdén and U. Lindenberger in *Frontiers in Aging Neuroscience,* Vol. 2, Article 27; 2010.

Life-Span Cognitive Activity, Neuropathologic Burden, and Cognitive Aging. R. S. Wilson, P. A. Boyle, L. Yu, L. L. Barnes, J. A. Schneider and D. A. Bennett in *Neurology,* Vol. 81, No. 4, pages 314–321; July 23, 2013.

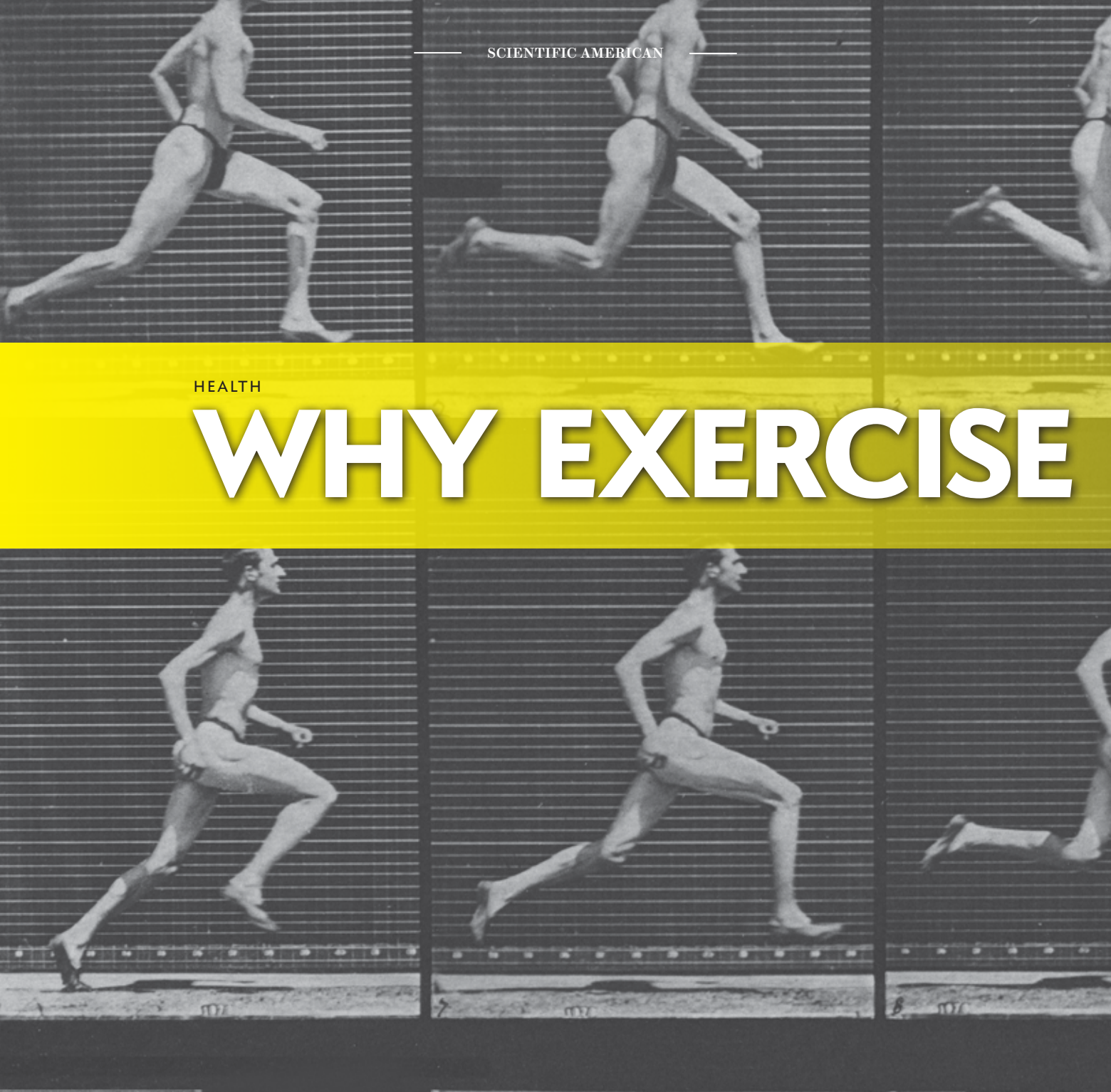
Bridging Animal and Human Models of Exercise-Induced Brain Plasticity. M. W. Voss, C. Vivar, A. F. Kramer and H. van Praag in *Trends in Cognitive Sciences,* Vol. 17, No. 10, pages 525–544; October 2013.

scientificamerican.com/magazine/sa

© 2015 Scientific American

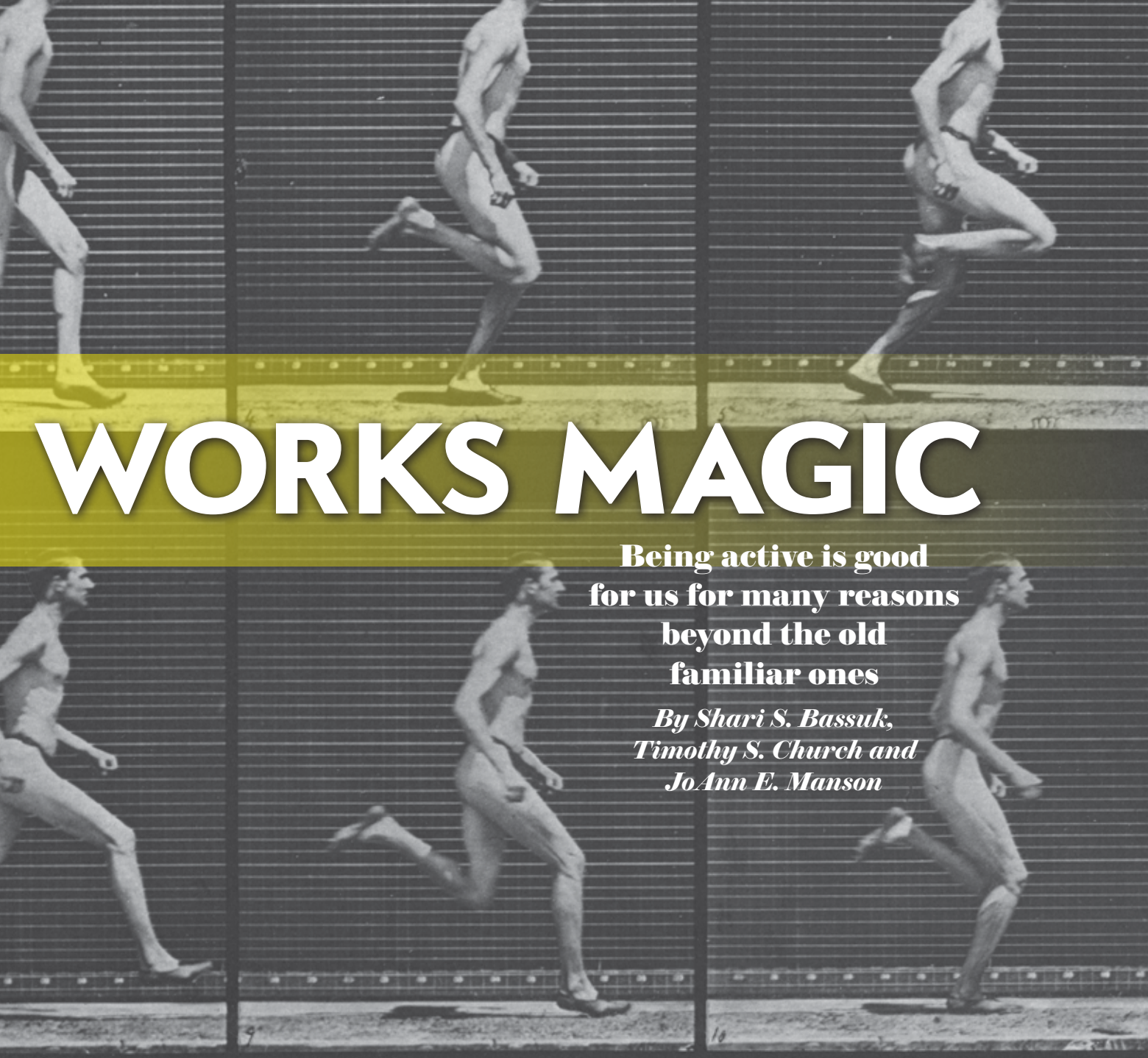
HEALTH

WHY EXERCISE



FIRST STEPS: In the 1800s Eadweard Muybridge perfected stop-motion photography to study human locomotion.

© 2015 Scientific American



WORKS MAGIC

Being active is good for us for many reasons beyond the old familiar ones

By Shari S. Bassuk, Timothy S. Church and JoAnn E. Manson

© 2015 Scientific American

WE ALL KNOW WE SHOULD EXERCISE. BUT FEW REALIZE THAT BEING PHYSICALLY active is the single most important thing that most of us can do to improve or maintain our health. Regular movement not only lowers the risk of developing or dying from heart disease, stroke and diabetes, it also prevents certain cancers, improves mood, builds bones, strengthens muscles, expands lung capacity, reduces the risk of falls and fractures, and helps to keep excess weight in check. And those are just some of the more familiar effects.

An explosion in research over the past few years has extended those observations even further. Among other things, exercise appears to boost brainpower—specifically the ability to carry out tasks that require attention, organization and planning, reduce symptoms of depression and anxiety in some people, and enhance the immune system's ability to detect and fend off certain types of cancer. In addition, researchers are moving beyond describing the gross health benefits of regular physical movement to detailing the positive changes that occur at the level of cells and molecules for specific conditions such as atherosclerosis and diabetes.

Studies aimed at tracing the many ways, large and small, that various systems in the human body (cardiovascular, digestive, endocrine and nervous, to name just a few) are affected by exercise show that the benefits most likely result from minor to moderate improvements in many aspects of physiology, as opposed to large favorable effects on a small number of processes in particular cells and tissues.

Investigators have also come to realize that people need not be triathletes to reap exercise's benefits. Twenty years ago preventive health experts focused almost exclusively on the gains to be had from vigorous activity. Today they emphasize the value of sustained bouts of moderate movement as well. One of us (Manson) helped to demonstrate comparable benefits of moderate and vigorous exercise for several health outcomes in the large-scale Nurses' Health Study and the Women's Health Initiative. Based on data from these and other projects, the latest U.S. exercise guidelines (published in 2008) recommend the equivalent of at least 30 minutes of moderate activity, such as brisk walking, five or more days a week (or 75 minutes of vigorous activity, such as jogging, each week), plus 30 minutes of muscle-strengthening activity at least two days a week.

A closer look at some of the most exciting findings offers a taste of the less obvious ways that exercise protects our body and keeps it running well.

IMMEDIATE EFFECTS

TO FULLY GRASP the latest findings, it helps to know something about how the body generally responds to increased physical

IN BRIEF

Routine physical activity of moderate or vigorous intensity substantially reduces the risk of dying from heart disease, stroke, diabetes, cancer and other ills.

Investigators have recently identified numerous previously unknown ways in which habitual exercise can reduce the risk of heart disease and cancer, can help control diabetes and can even facilitate learning.

Prolonged sitting may, however, cancel some of the health advantages gained through regular exercise.

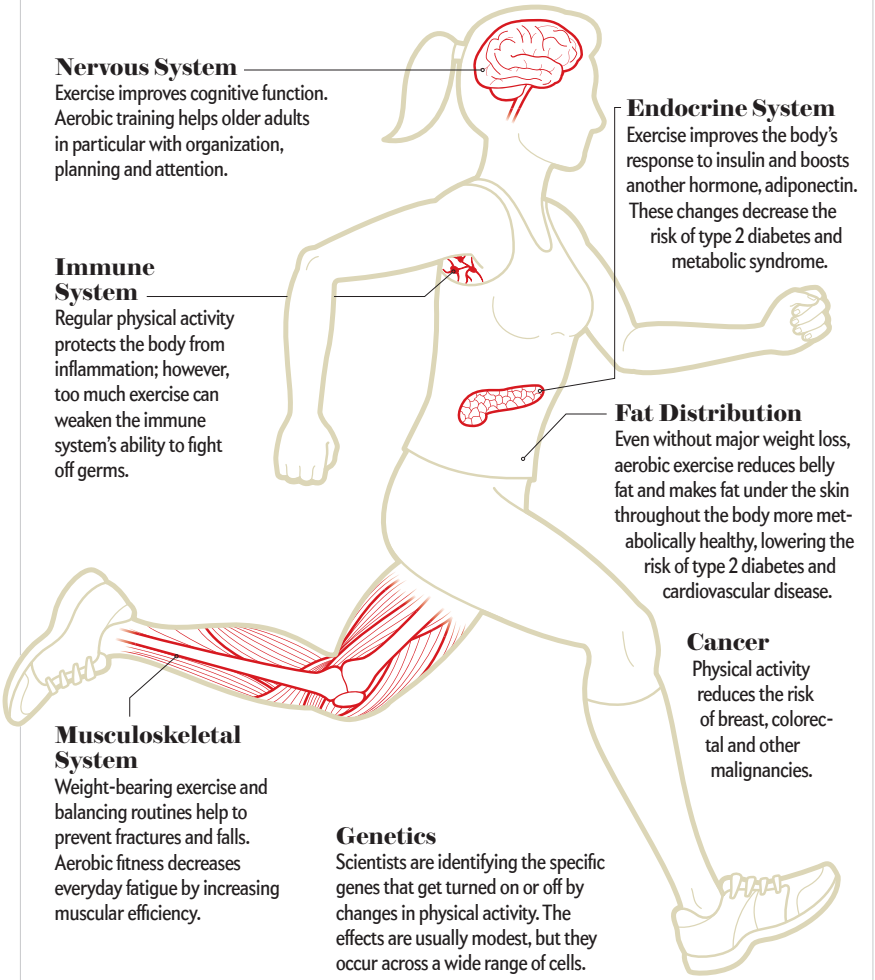
PRECEDING PAGES: EADWEARD MUYBRIDGE *University of Pennsylvania Archives*

© 2015 Scientific American

BEYOND THE HEART AND LUNGS

Exercise Benefits Even Obscure Parts of the Body

Most people do not realize that sustained bouts of moderate to vigorous physical activity completely change our bodies from the inside out. Here is a look at a few of the less widely known effects, starting with the neural connections in the brain and extending all the way out to the major muscles and bones of the limbs.



Nervous System
Exercise improves cognitive function. Aerobic training helps older adults in particular with organization, planning and attention.

Endocrine System
Exercise improves the body's response to insulin and boosts another hormone, adiponectin. These changes decrease the risk of type 2 diabetes and metabolic syndrome.

Immune System
Regular physical activity protects the body from inflammation; however, too much exercise can weaken the immune system's ability to fight off germs.

Fat Distribution
Even without major weight loss, aerobic exercise reduces belly fat and makes fat under the skin throughout the body more metabolically healthy, lowering the risk of type 2 diabetes and cardiovascular disease.

Cancer
Physical activity reduces the risk of breast, colorectal and other malignancies.

Musculoskeletal System
Weight-bearing exercise and balancing routines help to prevent fractures and falls. Aerobic fitness decreases everyday fatigue by increasing muscular efficiency.

Genetics
Scientists are identifying the specific genes that get turned on or off by changes in physical activity. The effects are usually modest, but they occur across a wide range of cells.

demands. Exercise means different things to different people. From snowshoeing to swimming to a fast walk on the beach, exercise can take many forms and occur at differing levels of intensity. Aerobic exercise is the type that significantly boosts the amount of oxygen needed by the muscles, requiring the lungs to work harder. Its health benefits are also the best understood. But more stationary forms of exercise—such as lifting weights or practicing one's balance—also have their place.

Scientists have developed fairly rigorous methods for measuring the intensity of aerobic exercise in research laboratories. An effective and much less expensive way to measure how much you are pushing your body outside the lab is the talk test. Moderate activity begins when your heart starts beating faster and you are breathing more heavily. You are still at a moderate level if you can talk or recite a poem while you are moving. If you can croak out only a word or two at a time, then you are exercising vigorously. At the other end of the scale, if you can sing while moving, then you are working at a light level of intensity.

Whenever a person picks up the pace, the nervous system prepares all the body's organs for action. Initially the individual may notice a heightened sense of awareness, increased heart rate, quickened breathing and light sweating. Internally, blood flow is reduced to those organs, such as the gastrointestinal tract and kidneys, that are not essential for movement. At the same time, blood vessels in the active muscles open up, ensuring that enough oxygen-rich blood flows to those muscles that are working the most.

Once in the muscle cells, oxygen diffuses into cellular structures called mitochondria, which use it to generate energy for the cell. The basic fuel for this process is the sugar molecule glucose, which the body creates through the breakdown of larger food particles and absorbs during the course of digestion. The addition of oxygen to glucose in mitochondria triggers a highly efficient kind of combustion. When oxygen is available, mitochondria can create nearly 20 times more energy per glucose molecule than they can in the absence of oxygen.

The body first burns up glucose molecules that are stored in the form of a compound called glycogen, found primarily in the liver and muscles. But as exercise continues, the available stock of glycogen is depleted and molecules of triglyceride (which is a kind of fat) become the chief source of fuel. All this internal combustion produces certain byproducts, such as lactic acid and carbon dioxide, which seep from the muscles into the bloodstream, where they are sensed by the rest of the body. The increasing concentration of these wastes prompts further biochemical reactions in the brain, lungs and heart that eventually make removal of these compounds more efficient and less tiring.

The benefits of exercise really start to accumulate once physical activity becomes a routine habit. The body adapts to the increasing demands being placed on it, leading to increased stamina as individuals become more fit. For instance, the lungs process more oxygen as each breath becomes deeper and the heart pumps more blood with each beat. These adaptations, which typically begin to show up within a few weeks of meeting or exceeding the federal guidelines on physical activity, also lead to changes in biology that improve long-term health.

Illustration by Brown Bird Design

© 2015 Scientific American

MOLECULAR CHANGES

ENTIRE LIBRARIES could be packed with data demonstrating the effects of exercise on everything from major organ systems to how various genes are turned on or off. A few top-level conclusions are outlined in the infographic that accompanies this article [*see box on preceding page*]. But we will focus here on some of the newly discovered mechanisms that help to explain why exercise expands our cognitive capacities, improves our ability to control blood glucose levels and strengthens our cardiovascular system. These changes have a greater effect on the quality of daily life than almost any other exercise benefits.

Athletes have long known that exercise boosts their mood and mental health. And yet it was not until 2008 that scientists were able to directly measure the so-called runner's high—a sense of euphoria that occurs after prolonged exercise. Not only did they show that the brain released more endorphins (opioidlike hormones that evoke pleasurable feelings) during a long-distance run, they also determined that the compounds were active in regions of the brain responsible for strong emotions. (Previous work had detected an endorphin surge only in the bloodstream, which was unrelated to changes in the brain.)

REGULAR PROLONGED MOVEMENT—AT WHATEVER INTENSITY LEVEL CAN BE SAFELY MANAGED—SHOULD BE BUILT INTO EVERYONE'S DAILY HABITS AND PHYSICAL ENVIRONMENT.

More recently, investigators have focused on the chemical changes in the brain by which exercise enhances our ability to concentrate, think and make decisions. In 2011 a scientifically rigorous experiment—known as a randomized controlled trial—of 120 people in their 60s and 70s demonstrated that exercise increases the size of a part of the brain called the hippocampus. The study's authors noted that the specific portion of the hippocampus that was affected by exercise is one that allows people to remember familiar surroundings; it is also one of the few areas of the brain that makes new nerve cells—at least in rats. Newborn neurons are thought to help with distinguishing similar but different events and things. Animal studies have further shown that exercise increases the levels of the chemical responsible for triggering the growth of these new neurons—a molecule known as brain-derived neurotrophic factor, or BDNF. Most recently, animal studies have identified a protein produced in the hippocampus that is responsible for increasing BDNF expression and turning on genes related to cognition. Researchers are hoping to develop an injectable form of this protein, called irisin, that could eventually be used to boost brain-protecting pathways.

Now research is challenging what we thought we knew about how exercise prevents heart disease. Scientists initially believed that routine activity reduced cardiovascular risk largely by decreasing blood pressure and lowering the amount of LDL cholesterol (also known as the bad cholesterol) while raising the amount of HDL cholesterol (the good cholesterol) in the blood. This conclusion was only partly correct. Exercise does in fact lower blood pressure substantially for some individuals, but for most people this benefit of exercise is relatively small. Moreover, exercise—particularly resistance exercise, such as weight training—can raise HDL cholesterol, a change that typically takes several months to emerge, although the effect is fairly modest—on the order of a few percentage points.

Further investigation has shown that the more important LDL-related effect has to do with how exercise changes the molecule's properties as opposed to reducing the amount found in the blood. Technically speaking, LDL is not synonymous with cholesterol; rather it carries cholesterol through the bloodstream the way a delivery truck carries groceries. (Being made of fat, cholesterol cannot dissolve in the watery environment of the bloodstream, so it has to be packaged in something that can.) LDL particles also come in various sizes in the same way that groceries can be delivered in minivans or giant trucks.

Over the past several years a growing number of scientists have found that smaller LDL molecules are particularly dangerous. They have a tendency, for example, to lose electrons, which then ricochet around the blood vessels damaging other molecules and cells (think crazed driver behind the wheel of a beat-up van). Large LDL molecules, on the other hand, are much more stable and float through the bloodstream without crashing into anything (more akin to big, well-maintained trucks with professional drivers).

Studies now show that exercise increases the number of larger, safer LDL molecules while decreasing the number of small, dangerous ones, and it alters the ratio by boosting the activity of an enzyme called lipoprotein lipase in fat and muscle tissue. Two people with the same amount of cholesterol in their blood but different levels of physical activity could thus have very different risk profiles for cardiac disease. The couch potato would probably have a lot of small LDLs and very few if any large ones, whereas large LDL molecules would predominate in the active person's blood. And yet despite having an identical cholesterol level, the first person would have several times the risk of suffering a heart attack of the second person.

Regular physical activity positively affects another key component of the blood—the sugar glucose. The liver, pancreas and skeletal muscles normally work together seamlessly to make sure that each part of the body gets the sugar it needs, whether you are at rest or active. By definition, exercise places increased demands on the skeletal muscles, which need increasing amounts of glucose to fuel their efforts. Over the long term, exercise also prompts the fibers within the muscle to become more efficient at using glucose, making the muscle stronger.

The liver responds immediately to the call for more fuel by churning sugar molecules into the bloodstream, and the pancreas releases a hormone called insulin that signals the cells to draw increasing amounts of glucose out of the blood. You might imagine that the whole process could lead to wild swings in glucose levels, but the body works hard to keep its blood sugar levels within a fairly limited range of between 70 and about 140 milligrams per deciliter (and well below 126 mg/dL in the fasting state)—at least in folks without diabetes. One reason that blood sugar needs to stay above 70 mg/dL is that the brain depends heavily on glucose as its primary source of fuel and thus is acutely sensitive to any change in the amount found in the blood. Although extremely

© 2015 Scientific American

low glucose levels can lead to coma and death in a matter of minutes, it is just as important not to spend long periods at the high end of the scale. Broadly speaking, extra sugar in the blood tends to gum up the works, causing cells to age prematurely.

As exercise becomes more of a daily habit, the muscles grow more sensitive to the effects of insulin. That means the pancreas does not have to work as hard to help keep glucose levels in check; lower levels of insulin will accomplish the same result as higher amounts once did. Doing more with less insulin is particularly helpful for people with type 2 diabetes, whose bodies have trouble keeping blood sugar in the normal range, in large part because they have become resistant to the hormone's effects. But insulin also promotes the proliferation, or rapid production, of new cells—and as such, elevated levels have been linked to a greater risk for developing breast and colon cancer in particular.

Recently physical activity has also been shown to promote the uptake of glucose through another pathway that does not require the presence of insulin. Having a second pathway to get glucose out of the bloodstream and into the muscle cells could open up new directions in the treatment of diabetes.

Intriguingly, the greatest benefits for people with diabetes seem to come from mixing different types of exercise. Two large randomized clinical trials have reported the combination of aerobic and resistance exercise is better at controlling blood glucose levels than either type of exercise alone. The first study was conducted in such a way, however, that it was unclear if the benefit came from the combination of exercise types or the fact that participants who underwent aerobic and resistance training also ended up exercising longer than their counterparts who followed a single exercise program. One of us (Church) decided to tackle that question by leading a second trial in which 262 previously sedentary men and women with diabetes were divided into four groups: an aerobic exercise group (who walked on a treadmill), a resistance group (seated rowing, leg presses, and the like), a combination group, and the control group, which undertook weekly stretching and relaxation classes.

Each of the groups who engaged in physical activity expended the same amount of time and effort (approximately 140 minutes per week) over the course of nine months. They also all lost inches off their waist, and both groups that performed aerobic exercise became more fit. But only the group that undertook both resistance and aerobic exercises exhibited a significant drop in their blood in the amount of a protein called HbA1c, which acts as an indicator of average blood glucose level over the past several months. The additive benefit suggests that aerobic and resistance training operate through different physiological mechanisms—an idea that investigators are actively pursuing.

Another way that continued exercise strengthens muscles is by boosting the formation of energy-producing mitochondria. In response to regular exercise, muscle cells start making a protein called PGC-1α, which directs the cells to churn out new mitochondria. More mitochondria mean each cell can convert more glucose into energy.

SITTING HAZARD

GIVEN THE MULTIPLE health benefits of moderate exercise, you might expect that everyone is lacing up their walking shoes and heading out the door. But many Americans fail to achieve even the recommended half an hour of moderate activity on five or more days of the week. Only 52 percent of U.S. adults are active enough to meet the aerobic exercise guideline, and 29 percent strengthen their muscles as recommended twice a week for 30 minutes at a time. One in five Americans meets the recommendations for both aerobic and resistance exercise.

The difficulties of changing people's sedentary habits have prompted scientists to investigate whether lighter or shorter bouts of exercise have any health benefits. Positive results, they hope, might motivate even couch potatoes to start moving more than they are used to doing. So far the data suggest that even minimal daily exercise routines can extend people's lives somewhat. A 2012 analysis of the data from six studies, totaling 655,000 adults in the U.S. who were tracked for about 10 years, found that people who expended as little as 11 minutes per day on leisurely activities (gardening, washing the car, taking an evening stroll) had a 1.8-year longer life expectancy after age 40 compared with their inactive peers. Admittedly, participants who met recommended guidelines for moderate activity were better off; their life expectancy was 3.4 years longer. And those who were active between 60 and 90 minutes each day achieved even greater gains (4.2 years longer life expectancy).

Despite the advantages of minimal efforts, a comprehensive look at exercise studies to date shows that most people would benefit from ramping up their activity—for example, adding moderate activity if they are light exercisers or short bursts of vigorous activity if they are moderate exercisers. Perhaps the worst news for today's office-bound knowledge workers is that sitting for more than six hours a day during leisure time may prove harmful even if you also manage a few high-intensity workouts. Still unknown: whether it is something about sitting itself that is a problem or the lack of movement usually associated with it.

Given the continual and growing evidence for the health benefits of physical activity, the message is clear. Regular prolonged movement—at whatever intensity level can be safely managed—needs to be built into everyone's daily habits and physical environments. It should become as easy as jumping into a car is now.

We strongly recommend that doctors and other health care providers regularly write a prescription for exercise during routine office visits. In addition, we advocate for increased research into the kinds of behavioral programs, public health campaigns and changes in urban design that will facilitate sustained levels of beneficial physical activity in our largely sedentary society. SA

Shari S. Bassuk is an epidemiologist at Brigham and Women's Hospital and a research associate at Harvard Medical School. **Timothy S. Church** is director of the preventive medicine research laboratory and professor at the Pennington Biomedical Research Center at Louisiana State University and chief medical officer at ACAP Health. **JoAnn E. Manson** is chief of the division of preventive medicine at Brigham and Women's Hospital, professor of medicine and Michael and Lee Bell Professor of Women's Health at Harvard Medical School, and professor in the department of epidemiology at the Harvard School of Public Health.

MORE TO EXPLORE

Global Recommendations on Physical Activity for Health. World Health Organization, 2010. http://whqlibdoc.who.int/publications/2010/9789241599979_eng.pdf

Physical Activity Guidelines for Americans: www.health.gov/paguidelines

© 2015 Scientific American

METABOLISM

KILLER CHAIRS

Standing more, even at a desk job, could lower risk for obesity, illness and death, studies suggest

By James Levine

CHAIRS: WE SIT IN THEM, WORK in them, shop in them, eat in them and date in them. Americans sit for most of their waking hours, 13 hours every day on average. Yet chairs are lethal.

This grim conclusion may surprise you, but 18 studies reported during the past 16 years, covering 800,000 people overall, back it up. In 2010, for example, the journal *Circulation* published an investigation following 8,800 adults for seven years. Those who sat for more than four hours a day while watching television had a 46 percent increase in deaths from any cause when compared with people who sat in front of the tube for less than two hours. Other researchers have found that sitting for more than half the day, approximately, doubles the risk of diabetes and cardiovascular problems. In one study, when researchers combined all causes of death and compared any group of sitters with those who were more active, sitters had a 50 percent greater likelihood of dying during about 8.5 years of follow-up.

Sitting for long periods is bad because the human body was not designed to be idle. I have worked in obesity research for several decades, and my laboratory has studied the effect of sedentary lifestyles at the molecular level all the way up to office design. Lack of movement slows metabolism, reducing the amount of food that is converted to energy and thus promoting fat accumulation, obesity, and the litany of ills—heart disease, diabetes, arthritis, and more—that come with being overweight. Sitting is bad for lean people, too. For instance, sitting in your chair after a meal leads to high blood sugar spikes, whereas getting up after you eat can cut those spikes in half.

The public usually associates these health problems with eating too much, not with sitting too much. My experience with people who struggle with their weight has led me to think that sitting habits might be just as pernicious. Still, a sedentary way of life might be easier to change than eating habits.

Peter (not his real name), a client in one of my programs in Minneapolis, told me, "I'm stuck." He was 44 years old, 50 pounds overweight and had type 2 diabetes. His doctor wanted him to start insulin injections. I sent him to my lab at the Mayo Clinic. There he watched the data as we measured his metabolic rate: strolling at less than two miles per hour increased his energy expenditure by 200 calories an hour. Afterward, Peter and I walked and talked. "Just by conducting two of your daily meetings strolling like this," I explained to him, "you'll burn 400 extra calories a day."

Peter took the advice to heart and began these easy walks. He did not diet, yet in the first year after his assessment, he lost 25 pounds. He dropped 10 more the next year. Peter never needed insulin and—as happens in many diabetics who lose weight—stopped taking diabetes medications altogether. He took this "get up" message home: he started going on bicycle rides and art gallery strolls with his family.

Peter is not alone in his success. Many studies support the view that simple movement has dramatic health effects. What is more, the effects do not require thrice-weekly visits to the gym or daily jogs that people soon abandon when the regimens become inconvenient. Nonexercise motion, done for several periods a day, can do the trick. And workers, companies and schools have already begun to institute an array of measures that encourage employees to get up out of their chairs.

MAGIC UNDERWEAR

MUCH OF THE EVIDENCE for the benefits of simple standing and walking during the day grew out of studies my group has con-

Illustration by Scott Brundage

© 2015 Scientific American

ducted since 2001 to compare people in agricultural communities with those, like Peter, who live in industrial, urban settings. To measure sitting and moving, we took Spandex underwear and added tiny posture and motion sensors that captured body movement in 13 directions every half a second for 10 days. Jokingly, my colleagues and I call this apparel "magic underwear," but it collects a serious amount of data.

We asked villagers living around a banana plantation in Jamaica, city dwellers in the island's capital, Kingston, and urbanites in the U.S. to wear the togs for 10 days. Among our findings: People who live in rural areas in Jamaica walk twice as much as even lean people living in Kingston and modern cities in the U.S. Those in agricultural communities sit for only three hours a day, whereas office workers can sit for 15 hours a day—and as people age, they sit even more. Because of this increased activity, as we noted in a 2011 article published in *Urban Studies,* agricultural work burns 2,000 calories more a day than many office jobs.

I was intrigued by the idea that converting sitting time to walking time could use so many calories. I called this phenomenon "nonexercise activity thermogenesis," or NEAT. NEAT is the energy a person expends going about his or her everyday life. And I wondered if it made a difference in the weight of people with similar kinds of jobs and surroundings, not just our agricultural and urban workers.

For a hint, we compared lean and obese people in the U.S. who lived in similar environments and had similar diets and jobs. We had our subjects don the magic underwear, and it revealed that obese people sit 2.25 hours longer than their lean counterparts every day. These sedentary obese people expended 350 calories fewer a day through walking and other NEAT activities than did lean people.

The pattern was suggestive but not definitive. To see if low levels of these nonexercise activities could cause weight gain, we began what came to be known as the "Great Gorging Experiment." We asked 16 lean volunteers to overeat while we monitored them carefully. Every day for eight weeks, each volunteer received 1,000 calories a day beyond their normal energy needs.

Some of our volunteers were like those frustrating friends—we all seem to have them—who do not put on weight despite continuous doughnut consumption. These volunteers gained almost no body fat after eight weeks and a total of 56,000 extra calories. How did they stay thin? Our underwear sensors showed they increased their NEAT levels, although none of them said they made a conscious effort to do so. In contrast, other overfed volunteers deposited almost every extra calorie in their body fat. The reason that these volunteers gained so much fat was that they did not change their NEAT—they remained stuck to their chairs, as we reported in *Science* in 1999.

These people were ignoring a drive to move that is as biological as breathing. In animals, movement enables aggressors to chase, the threatened to flee, the forager to search, and the reproductive to find mates. Rodent experiments show that there is intricate brain circuitry that monitors and responds to calorie expenditure, activity and rest. It is located in an area called the hypothalamus, which also regulates such functions as temperature and sleep-wake cycles.

Moreover, investigators have determined over the past decade that part of the hypothalamus manages appetite and will make you hungry if you spend a whole day raking leaves. Meanwhile a feedback system from the muscles senses muscular overexertion and signals a person to sit and rest. The modern chair-based environment has overwhelmed this biologically driven balancing act.

WHAT CAN WE DO?

WE ARE NOT, however, prisoners of this environment. We can break free. Although technologies such as computers and video games have contributed to the allure of the chair, technology can also be a part of the solution. The cell phone, for instance, enables a seated conversation to become a walking talk. A host of popular activity-sensing gadgets enable people to measure how often they sit or stand or move. Newer video games, called Exergames, link computers to physical competitions; the Nintendo Wii, which encourages movement, was a game changer here.

Work can become more active as well. On behalf of some corporations, my lab has redesigned workplaces that release employees from their chair-based isolation. One company in St. Paul, Minn., encouraged walk-and-talk meetings by taping walking tracks to its carpets. A firm in Iowa discouraged workers from sending e-mail to their colleagues nearby by creating "e-mail-free work zones"; computer networks can block e-mail to close-by desktops.

A decade ago I came up with the idea of a treadmill desk as a way to allow office workers to do their jobs while moving. The unit allows people to walk while conducting business. A computer is placed on a high table with a slow-speed (1 to 2 mph) treadmill underneath it. A person can stroll while typing, answering e-mails and taking phone calls. Naturally, as the inventor, I think the desk is a good idea, and I was pleased when a study published in *Health Services Management Research* in 2011 reported that people who use the desks are slimmer, are less stressed, and have lower blood pressure and cholesterol levels. The treadmill desk, of course, is not the only way to incorporate more activity into your day.

As is true of offices, schools can become more active places. We helped to build a classroom in Rochester, Minn., where students practiced spelling while strolling and mathematics while throwing balls. In Idaho Falls a classroom was redesigned so that all the sit-down desks were replaced with standing desks that had a "fidget bar" for students to swing their legs on. Studies show that enrollees in schools that promote movement are twice as active as those attending traditional schools. Educational test scores also improve by about 10 percent, and their hormone levels are in healthier ranges.

Cities can be reimagined to encourage movement. Analyses conducted in San Francisco and the U.K. demonstrate that city districts can be rezoned to discourage car-based travel. Commute times increase by only a handful of minutes, air quality improves, and medical expenses drop. Chair-free living does not just promote health but also saves money.

We live amid a sea of killer chairs: adjustable, swivel, recliner, wing, club, chaise longue, sofa, arm, wood, leather, plastic, car, plane, train, dining and bar. That's the bad news. The good news is that you do not have to use them. Pat yourself on the back if you read this article standing up—and if you didn't, get up! SA

James Levine is an endocrinologist who co-directs Obesity Solutions, a program of the Mayo Clinic in Scottsdale, Ariz., and Arizona State University. He is author of the book *Get Up!* (Palgrave Macmillan, 2014). (Scientific American and Palgrave Macmillan are affiliates.) Levine invented a treadmill desk but gains no financial benefit from sales.

© 2015 Scientific American

CALORIES

IS FASTING GOOD FOR YOU?

Intermittent fasting might improve health, but clinical data are thin

By David Stipp

IN THE BELOVED NOVEL *CHARLOTTE'S Web,* by E. B. White, an old sheep advises the gluttonous rat Templeton that he would live longer if he ate less. "Who wants to live forever?" Templeton sneers. "I get untold satisfaction from the pleasures of the feast."

It is easy to empathize with Templeton, but the sheep's claim has some merit. Studies have shown that reducing typical calorie consumption, usually by 30 to 40 percent, extends life span by a third or more in many animals, including nematodes, fruit flies and rodents. When it comes to primates and people, however, the picture is unclear. One long-term study of calorie-restricted rhesus monkeys showed that the stringent diets increased survival; another such study, published in 2012, surprisingly failed to show that. Yet a 2014 report suggested that the control monkeys in the latter study, which supposedly were not calorie-restricted, were actually on diets tantamount to mild calorie restriction. That may account for the study's failure to show a significant longevity difference between its controls and experimental animals. Even if calorie restriction does not help anyone live longer, a large portion of the data supports the idea that limiting food intake reduces the risks of diseases common in old age and lengthens the period of life spent in good health.

If only one could claim those benefits without being hungry all the time. There might be a way. In recent years researchers have focused on a strategy known as intermittent fasting as a promising alternative to continuous calorie restriction.

Intermittent fasting, which includes everything from periodic multiday fasts to skipping a meal or two on certain days of the week, may promote some of the same health benefits that uninterrupted calorie restriction promises. The idea of intermittent fasting is more palatable to most people because, as Templeton would be happy to hear, one does not have to renounce the pleasures of the feast. Studies indicate that rodents that feast one day and fast the next often consume fewer calories overall than they would normally and live just as long as rodents eating calorie-restricted meals every single day.

In a 2003 mouse study overseen by Mark P. Mattson, head of the National Institute on Aging's neuroscience laboratory, mice that fasted regularly were healthier by some measures than mice subjected to continuous calorie restriction; they had lower levels of insulin and glucose in their blood, for example, which signified increased sensitivity to insulin and a reduced risk of diabetes.

THE FIRST FASTS

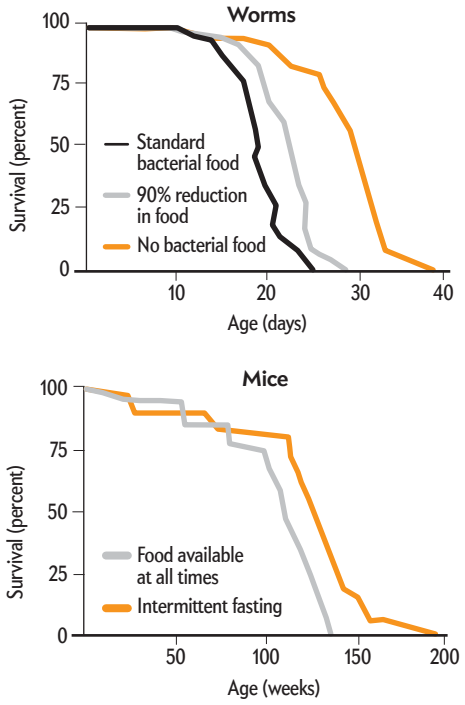
RELIGIONS HAVE LONG maintained that fasting is good for the soul, but its bodily benefits were not widely recognized until the early 1900s, when doctors began recommending it to treat various disorders—such as diabetes, obesity and epilepsy.

Related research on calorie restriction took off in the 1930s, after Cornell University nutritionist Clive McCay discovered that rats subjected to stringent daily dieting from an early age lived longer and were less likely to develop cancer and other diseases as they aged, compared with animals that ate at will. Research on calorie restriction and periodic fasting intersected in 1945, when University of Chicago scientists reported that alternate-day feeding extended the life span of rats as much as daily dieting in McCay's earlier experiments. Moreover, intermittent fasting "seems to delay the development of the disorders that lead to death," the Chicago researchers wrote.

In the next decades research into antiaging diets took a backseat to more influential medical advances, such as the continued development of antibiotics and coronary artery bypass surgery.

Photoillustration by Kelly Blair

© 2015 Scientific American



FASTING BOOSTS SURVIVAL: Fasting has extended life span in post–larval stage worms (*top*) and mice (*bottom*). Such studies have also provided evidence that intermittent fasting staves off common age-related diseases in animals.

More recently, however, Mattson and other researchers have championed the idea that intermittent fasting probably lowers the risks of degenerative brain diseases in later life. Mattson and his colleagues have shown that periodic fasting protects neurons against various kinds of damaging stress, at least in rodents. One of his earliest studies revealed that alternate-day feeding made the rats' brains resistant to toxins that induce cellular damage akin to the kind cells endure as they age. In follow-up rodent studies, his group found that intermittent fasting protects against stroke damage, suppresses motor deficits in a mouse model of Parkinson's disease and slows cognitive decline in mice genetically engineered to mimic the symptoms of Alzheimer's disease. A decidedly slender man, Mattson has long skipped breakfast and lunch except on weekends. "It makes me more productive," he declares. The 57-year-old researcher, who has a Ph.D. in biology but not a medical degree, has written or co-authored more than 700 articles.

Mattson thinks that intermittent fasting acts in part as a form of mild stress that continually revs up cellular defenses against molecular damage. For instance, occasional fasting increases the levels of "chaperone proteins," which prevent the incorrect assembly of other molecules in the cell. Additionally, fasting mice have higher levels of brain-derived neurotrophic factor (BDNF), a protein that prevents stressed neurons from dying. Low levels of BDNF have been linked to everything from depression to Alzheimer's, although it is still unclear whether these findings reflect cause and effect. Fasting also ramps up autophagy, a kind of garbage-disposal system in cells that gets rid of damaged molecules, including ones that have been previously tied to Alzheimer's, Parkinson's and other neurological diseases.

One of intermittent fasting's main effects seems to be increasing the body's responsiveness to insulin, the hormone that regulates blood sugar. Decreased sensitivity to insulin often accompanies obesity and has been linked to diabetes and heart failure; long-lived animals and people tend to have unusually low insulin, presumably because their cells are more sensitive to the hormone and therefore need less of it. A 2012 study at the Salk Institute for Biological Studies in La Jolla, Calif., showed that mice that feasted on fatty foods for eight hours a day and subsequently fasted for the rest of each day did not become obese or show dangerously high insulin levels.

The idea that periodic fasting may offer some of the same health benefits as continuous calorie restriction—and allows for some feasting while slimming down—has convinced an increasing number of people to try it, says Steve Mount, a University of Maryland genetics professor who has moderated a Yahoo discussion group on intermittent fasting for more than nine years. Intermittent fasting "isn't a panacea—it's always hard to lose weight," adds Mount, who has fasted three days a week since 2004. "But the theory [that it activates the same signaling pathways in cells as calorie restriction] makes sense."

ON THIN GROUND

DESPITE THE GROWING enthusiasm for intermittent fasting, researchers have conducted few robust clinical trials, and its long-term effects in people remain uncertain. Still, a 1956 Spanish study sheds some light, says Louisiana-based physician James B. Johnson, who co-authored a 2006 analysis of the study's results. In the Spanish study, 60 elderly men and women fasted and feasted on alternate days for three years. The 60 participants spent 123 days in the infirmary, and six died. Meanwhile 60 nonfasting seniors racked up 219 infirmary days, and 13 died.

In 2007 Johnson, Mattson and their colleagues published a clinical study showing a rapid, significant alleviation of asthma symptoms and various signs of inflammation in nine overweight asthmatics who near-fasted every other day for two months.

Detracting from these promising results, however, the literature on intermittent fasting also includes several red flags. A 2011 Brazilian study in rats suggests that long-term intermittent fasting increases blood glucose and tissue levels of oxidizing compounds that could damage cells. Moreover, in a 2010 study co-authored by Mattson, periodically fasting rats mysteriously developed stiff heart tissue, which in turn impeded the organ's ability to pump blood.

And some weight-loss experts are skeptical about fasting, citing its hunger pangs and the possible dangers of compensatory gorging.

Still, from an evolutionary perspective, three meals a day is a strange modern invention. Volatility in our ancient ancestors' food supplies most likely brought on frequent fasting—not to mention malnutrition and starvation. Yet Mattson believes that such evolutionary pressures selected for genes that strengthened brain areas involved in learning and memory, which increased the odds of finding food and surviving. If he is right, intermittent fasting may be both a smart and smartening way to live. SA

David Stipp is a Boston-based science writer who focuses on aging research. He is author of *The Youth Pill: Scientists at the Brink of an Anti-Aging Revolution* (Current, 2010).

SOURCE: "FASTING: MOLECULAR MECHANISMS AND CLINICAL APPLICATIONS," BY VALTER D. LONGO AND MARK P. MATTSON, IN *CELL METABOLISM REVIEW*, VOL. 19; FEBRUARY 4, 2014

© 2015 Scientific American

PSYCHOLOGY

MORTAL THOUGHTS

We run from the subject like there's no tomorrow, but thinking about death can ease our angst and make us better people, too

By Michael W. Wiederman

MY FATHER WAS JUST 32 YEARS OLD WHEN HE WAS DIAGNOSED WITH ACUTE LEUKEMIA. Weeks later he was in the hospital, informed that he would not be leaving. Miraculously the leukemia went into remission, and he lived another five years. Even as a child, though, I could clearly see that the man who returned from the hospital was not the same one who had left home. Before, he had been concerned mostly with work and material success; now he embraced religion and family. Getting a second, tenuous chance at life was a profound experience that deeply changed his values and behavior.

IN BRIEF

Awareness of our mortality has different effects depending on whether the awareness is conscious and reflective or subconscious and fleeting. Prolonged contemplation of death produces shifts in personal values and goals.

Terror Management Theory proposes that we unconsciously fend off thoughts of our mortality by investing in our culture as a symbolic way of attaining some degree of immortality.

A large body of research has shown that subconscious awareness of mortality prompts people to defend their worldviews, even in ways that may be harmful.

Facing death head-on may enable us to pursue meaning in life and to handle mortality more easily.

ISTOCKPHOTO (leaf); DUANE RIEDER Getty Images (man holding leaf)

© 2015 Scientific American

© 2015 Scientific American

REMEMBERING THAT I'LL BE DEAD SOON IS THE MOST IMPORTANT TOOL I'VE EVER ENCOUNTERED TO HELP ME MAKE THE BIG CHOICES IN LIFE. —STEVE JOBS

JOE BARAN Getty Images

FUTURE SHOCK: A close brush with death or the death of a loved one can prompt us to reassess our lives.

We deflect it with humor, hedge against it with good works, shun reminders of our animal nature. Yet we all share the reality of mortality, and we know it, try as we might to throttle our thoughts about it. Indeed, this simultaneous knowing and recoiling from our knowledge is a tension that will run throughout our life. Yet despite the significance of the subject, for most of its history psychology has left the matter of how mortal thoughts affect us almost completely unexplored—terror incognita.

That neglect appears to be a thing of the past. In recent years researchers have begun to find that awareness of mortality affects our behavior in ways both overt and subtle and sometimes seems to pull us in opposite directions. Therapists who take an existential approach to counseling have found that confrontation with our mortality is worthwhile and beneficial. At the same time, a new discipline called Terror Management Theory (TMT) has spawned hundreds of studies showing that awareness of our mortality can lead to selfish, even hurtful behavior.

More recently, this apparent disagreement among different disciplines, common enough in new fields of research, has given way to a deeper understanding of why our thoughts about mortality sometimes help us and sometimes do us harm. One essential determinant of how we handle the subject appears to be whether our life goals are material or idealistic. The effect of mortal thinking on behavior also seems to depend on whether death is at the top of our mind or hovering just beyond our consciousness. Still, the duality of helpful and harmful effects echoes one of life's central conundrums: we cannot deny that someday we will die, so how are we to keep this paralyzing truth from paralyzing us?

FACING DEATH HEAD-ON

IN ONE OF MY FAVORITE CARTOONS, by Eric Lewis, a man lying on his deathbed says to his attentive wife, "I should have bought

© 2015 Scientific American

THE ONLY WAY I EXPECT TO HAVE SOME VERSION OF IMMORTALITY IS THROUGH MY BOOKS. —ISAAC ASIMOV

NEXT GEN: Parenthood provides us with a sense of purpose and symbolic immortality that can help stave off existential angst.

GARY JOHN NORMAN *Getty Images*

more crap." The dying man's regret is a tour de force of deflection and misdirection, the opposite of what we expect of a man looking back with rue. For most of us, a near-death experience or the death of someone we know prompts us to take stock of our life in a good way. This certainly was true for my father, and it is precisely the effect that existential therapists count on as they try to help their clients confront mortality and shift their life onto a more meaningful path. Typically the shift is from extrinsic values and goals, such as material success, toward intrinsic ones, such as matters of the soul or spirit.

Surveys validate the usefulness of the approach. In a study published in 2007 Emily L. B. Lykins, now at Eastern Kentucky University, and her colleagues questioned staff at a medical center in Northridge, Calif., two to three weeks after an earthquake in 1994 devastated the surrounding area, killing 57 and injuring thousands more. The staff were asked to rate the importance of 16 different goals both currently and as they were before the earthquake. The results indicated a shift in values toward intrinsic goals such as cultivating close relationships, doing creative work and developing as a person. Moreover, those respondents who had most strongly feared they were going to die in the earthquake were also most likely to indicate a shift from extrinsic to intrinsic goals.

The beneficial effect works the other way around, too. People who pursue intrinsic goals have more success in heading off anxiety associated with death than those who chase material things. In 2009 Alain Van Hiel and Maarten Vansteenkiste of Ghent University in Belgium published their survey of older adults (with an average age of 75). The elders who reported having fulfilled more of their intrinsic goals were the least anxious about death and most satisfied with their life. In contrast, respondents who reported the greatest attainment of extrinsic goals indicated the most despair and the least acceptance of death.

Intrinsic life goals and the creation of meaning appear to be central to coping with our mortality. In 2012 William S. Breitbart and several colleagues at Memorial Sloan-Kettering Cancer Center in New York City published the results of an intervention with patients coping with advanced stages of cancer. The patients were randomly invited to participate in one of two groups that met once a week for eight weeks. The first group, which focused on social support, facilitated discussions about day-to-day concerns and ways to cope with them. The second group focused on the sources of meaning in life. At the end of the eight weeks and again at a two-month follow-up, members of the group focused on meaning in life showed substantial increases in their scores on measures of meaning, peace and faith, along with decreases in anxiety and desire for death. The members of the group focused on social support showed no statistically significant changes.

TAMING TERROR

THESE SURVEYS SUGGEST that people who have an abrupt encounter with mortality tend to seek meaning in life, and those who pursue meaning in life can handle mortality more easily. People also seem to use systems of meaning to block awareness of their mortality, clinging to aspects of their life that provide connection with social structures.

How this protective shield might work is the focus of the burgeoning field of Terror Management Theory. Based on the writings of cultural anthropologist Ernest Becker in the 1960s and 1970s and the more recent work of psychologists Jeff Greenberg of the University of Arizona, Tom Pyszczynski of the University of Colorado Colorado Springs and Sheldon Solomon of Skidmore College, TMT proposes that we humans maintain a shared culture because social roles and consequences for behavior keep us busy and so insulate us from the existential terror of our impermanence.

© 2015 Scientific American

I DON'T WANT TO ACHIEVE IMMORTALITY THROUGH MY WORK . . . I WANT TO ACHIEVE IT THROUGH MY NOT DYING. —WOODY ALLEN

Interesting as such propositions are, they leave unanswered the question of whether our thoughts of mortality are what spur us to defend our culture and bolster our self-esteem or whether we just do what we do because it feels right. Psychologists needed a new approach to tease out how our mortal thoughts influence us.

DEATH IN THE LABORATORY

IMAGINE YOU ARE STAYING with a friend who lives on the 20th floor of an old apartment building. It's the middle of the night. You are awakened from a deep sleep by the sound of screams and the choking smell of smoke. You run to the door and reach for the handle. You pull back in pain as the intense heat of the knob burns your skin. You grab a blanket from the bed for protection and manage to open the door. Almost immediately, a huge wall of flame and smoke roars into the room. It is getting very hard to breathe, and the heat from the flames is almost unbearable. You try calling out for help, but you can't find the air to form the words. With your heart pounding, it suddenly hits you that you are moments from dying. Out of breath and weak, you shut your eyes and wait for the end.

Fun thought exercise, yes? It is drawn from a 2003 study by Philip J. Cozzolino, now at the University of Essex in England, and his colleagues. Contemplating scenarios like it is how volunteers in some of the hundreds of TMT studies conducted during the past two decades were primed (and terrified) before they were put through their paces by researchers trying to see how reflection about death can affect human behavior.

SPIRIT: Religion can temper fear of mortality by providing believers with a strong sense of purpose and by giving death a context so that it no longer seems a great unknown.

BRAD WILSON *Getty Images*

Most TMT research focuses on the so-called mortality salience hypothesis: if investment in our culture and self-esteem serves to fend off our sense of mortality, then stimulating our awareness of mortality should increase investment in our culture and self-esteem. Researchers can arouse mortality salience in a variety of ways, but in most studies, participants are asked to write essays in which they imagine either death or some other kind of pain.

One group might be asked to visualize a scenario akin to the one above and to describe both what would happen to them physically as they died and the feelings kindled in them by thinking about their death. The control group might be asked to imagine and describe a less terminally uncomfortable event, such as an episode of dental pain or an experience of social exclusion. Then the researchers attempt to assess how the two groups differ in their self-esteem and their willingness to invest in their culture.

What researchers learned was that when thoughts of death reverberate too loudly, they can drown out subtle but important changes in our behavior. When we are made to concentrate on our mortality,

© 2015 Scientific American

AS A WELL-SPENT DAY BRINGS HAPPY SLEEP, SO A LIFE WELL USED BRINGS HAPPY DEATH. —LEONARDO DA VINCI

DARRYL DYCK/AP Photo

FLESH: Research suggests that people who have been primed to think about death are more likely to be uncomfortable at the sight of a mother breast-feeding in public.

we tend to defend against anxiety by direct means, primarily denial, rationalization and a focus on the positive aspects of our life, boosting our sense of well-being by converting death into an abstraction that lies in the far future. Thus, if scientists measure investment in worldview or self-esteem immediately after increases in awareness of mortality (as with the group writing about death by fire), usually they see no apparent effects. The relations appear only when respondents are distracted after their awareness is heightened.

In a typical study, after completing the death essay (or the control essay), participants perform a filler task having nothing to do with death so that any unconscious defenses against mortality awareness have a chance to emerge. Only then comes a measurement of the participants' investment in their culture or self-esteem. Within this framework, researchers began to see that our mortality affects us in ways we do not even realize, especially in how it can transform our goals.

RELIGIOSITY AND CREATURELINESS

BECAUSE RELIGION is such an important aspect of our worldview (not least whether we are pro or con), it makes an especially useful starting point for researchers. Religious teachings tend to explain what happens to believers and nonbelievers after death, so defending one's religious beliefs in the face of mortality is particularly common. Yet a series of studies reported in 2006 by psychologists Ara Norenzayan of the University of British Columbia and Ian G. Hansen of York College showed that thoughts of death did more than make people with religious dispositions think of eternity at the right hand of God.

In the first of their studies, college students randomly assigned to write the standard death essay rated themselves about 30 percent higher on measures of religiosity and belief in God than did students assigned to write the control essay. What the experiment did not reveal was whether thoughts of death simply reminded people of their religious belief or prodded them to bolster their religiosity as a defense against mortality. To investigate this possibility, the second study randomly exposed college students to one of three versions of a brief story about a boy's visit to a hospital. All versions started and ended the same, but the middle passages differed. In the control version, the boy watched an emergency drill carried out by adults, in the religious version the boy observed a man praying in the hospital chapel, and in the death version the boy had an accident and died.

One of the distraction tasks in the experiment called for students to read a report of a study illustrating apparent effects of Christian prayer by strangers on the reproductive rates of women attending a fertility clinic. As part of their assessments of the study, participants were asked to rate their belief in God or in a higher power. The ratings by students in the control condition and religious condition did not differ, but both were significantly lower than the ratings by those in the death condition. It seems that mortality salience uniquely motivates people to bolster their religious beliefs.

Besides giving us a context for spirituality, culture also helps to protect us from thoughts of mortality through norms and customs that let us forget we are animals, which we know are mortal and die for capricious reasons. For example, elimination of bodily waste is taboo and performed in private, and our clothing and grooming typically help us avoid the smell and look of wild creatures. Our dining manners and rituals keep us from "eating like an animal," a charge that is clearly an insult.

TMT proposes that experiences that remind us of our animal nature will arouse awareness of our mortality, thus causing us to avoid them, especially if mortality salience is already heightened. How we might feel about seeing a woman breast-feeding her infant, for instance, seems to be influenced by whether we have been made aware of our mortality beforehand.

In 2007 Cathy Cox, now at Texas Christian University, and her colleagues published their research on this question. In their first study, college students rated their reaction to a written scenario in which a woman breast-feeds in a fancy restaurant, provoking a negative reaction from the restaurant staff. Volunteers who had been primed with the death essay rated the woman 40 percent more

© 2015 Scientific American

YOU ONLY LIVE TWICE: ONCE WHEN YOU ARE BORN, AND ONCE WHEN YOU LOOK DEATH IN THE FACE. —IAN FLEMING

ENDGAME: Elderly people whose life goals were idealistic, such as the pursuit of meaningful work and relationships, tend to be less anxious about death than those who focused on material accomplishments.

harshly than did the students primed by the dental pain essay.

Cox and her colleagues followed up by bringing breast-feeding into the lab, although no actual breast-feeding occurred. The researchers told college student participants that the study involved formation of impressions of another person before completing a task with that person. The subjects were advised that the other participant was a young woman who could not find child care and had to bring her infant along with her; she had arrived early and was feeding the child in the other room.

The students were randomly told either that the mother was breast-feeding or bottle-feeding and then were randomly assigned either to the standard death essay or to the dental pain essay. After filling out a questionnaire about hobbies and interests, the students were presented with what they believed was a like questionnaire that had been completed by the young mother in the other room. In reality, there was no such person, and all students were shown the same fictitious profile. They were then asked to rate their impressions of this other student with whom they would soon be working.

When rating the likability of this mystery woman, students who had written about dental pain returned similar ratings whether the woman was described as bottle-feeding or breast-feeding. Yet those primed with the death essay rated the young mother as less likable when she was said to be breast-feeding. Last, the participants were told it was time to perform the joint task with the young mother. They were taken to an empty room containing only two folding chairs leaning against the wall and were asked to set up the chairs, facing each other, in preparation for the task. The researchers were looking to see how closely the students placed the chairs. The distances between the two chairs were very similar in all but one condition: the students placed the chairs about 20 percent farther apart when they had been primed with the death essay and told that their partner had been breast-feeding.

It appears that when primed to think about our own mortality, we tend to disparage and distance ourselves from reminders that we humans are animals. Other researchers have demonstrated this phenomenon with people's reactions to the elderly, disabled individuals and sexual activity. In an article published in 2000 the originators of TMT (Greenberg, Pyszczynski and Solomon) described research they conducted with their colleague Jamie Goldenberg, now at the University of South Florida. College students who underwent the standard method for inducing mortality salience rated the physical aspects of sex as less appealing compared with students who had not

JAY P. MORGAN Getty Images

© 2015 Scientific American

THERE IS NO CURE FOR DEATH, SAVE TO ENJOY THE INTERVAL. —GEORGE SANTAYANA

HORROR: Enjoying a violent movie or book can let us confront death vicariously while remaining safely insulated from our own mortality.

BEAU LARK *Corbis*

been so primed. The same researchers later found that students primed to focus on the romantic meaning of sex experienced fewer thoughts about death than did those primed to focus on the physical aspects of sex.

HANDLING DEATH

SO WHAT DOES ALL THIS TELL US about how we might manage our fear of mortality? If brushes with death help people worry less about it and devote more energy to the things that give deeper meaning to life, then focused thinking about death might help the rest of us.

We already expose ourselves to death without knowing why. We watch slasher films, read violent novels and news accounts of tragic deaths, and share sick jokes about death and corpses. Such diversions might appeal to us because vicarious experiences of death can satisfy curiosity and address our anxiety in a way that keeps our own mortality at a safe remove. In fact, by choosing exposure to death we exert a degree of control. Death becomes something that prompts a laugh, a groan or a thrill rather than terror. Culturally constructed scenarios of death may serve as a safety valve for venting anxiety.

Repeated exposure to death and dying in naturalistic settings also appears to lower discomfort around the topic. In 2008 Susan Bluck and her colleagues at the University of Florida published a study of hospice volunteers. Scores on a measure of death anxiety were lower for more experienced volunteers than for novices. Also, the best predictor of the level of their anxiety about death was not the length of time that the volunteers had served but the number of deaths that they had attended. Ironically, by prolonging human lives and removing our loved ones from their natural habitats when they are dying, medical technology has insulated us from experiences with death; greater anxiety about mortality may be a side effect.

One brief period of thinking about our mortality would probably do little good. Yet repeated contemplation of our eventual death could both lessen the anxiety about it and help keep us focused on the aspects of life that matter most.

Without such focused contemplation, thinking about the end of life is as likely to take us to the darkness as to the light. In a survey of nearly 1,000 students who took her Sociology of Death and Dying course at the University of Louisiana at Lafayette from 1985 to 2004, Sarah Brabant asked her students how often they thought about death. The most common responses were "occasionally" (58 percent) and "frequently" (20 percent). She also asked how the students felt when they thought of their own mortality. The two most common responses were "fearful" and "pleasure in being alive," each at 29 percent.

Within these few statistics lies the human condition. We cannot escape awareness of our mortality, and that awareness has the power to elicit fear or appreciation. Fortunately, the choice is ours. SA

Michael W. Wiederman is director of faculty development at the University of South Carolina School of Medicine–Greenville. He can be reached through his Web site: www.MindingtheMind.com

MORE TO EXPLORE

The Denial of Death. Ernest Becker. Free Press, 1973.
In the Wake of 9/11: The Psychology of Terror. T. Pyszczynski, S. Solomon and J. Greenberg. American Psychological Association, 2003.
On the Unique Psychological Import of the Human Awareness of Mortality: Theme and Variations. T. Pyszczynski, J. Greenberg, S. Solomon and M. Maxfield in *Psychological Inquiry,* Vol. 17, No. 4, pages 328–355; 2006.
Staring at the Sun: Overcoming the Terror of Death. Irvin D. Yalom. Josey-Bass, 2008.
Flight from Death: The Quest for Immortality. Film directed by Patrick Shen. Transcendental Media, 2009. www.FlightFromDeath.com
Death Anxiety and Its Role in Psychopathology: Reviewing the Status of a Transdiagnostic Construct. Lisa Iverach, Ross G. Menzies and Rachel E. Menzies in *Clinical Psychology Review,* Vol. 34, pages 580–593; 2014.

© 2015 Scientific American

© 2015 Scientific American

MEDICINE

ALZHEIMER'S: FORESTALLING THE DARKNESS

Interventions before symptoms appear could be key to slowing or stopping the leading cause of dementia

By Gary Stix

IN BRIEF

The incidence of Alzheimer's disease continues to rise as the population ages, but effective treatments are still lacking.

Almost all recent drug trials have ended in failure. Some might have come too late to affect the course of the disease.

New techniques to track the disease before symptoms arise, and to measure biological changes associated with successful therapies, may allow testing of drugs at a stage when they may be more efficacious.

ETHAN HILL

© 2015 Scientific American

IN HIS MAGICAL-REALIST MASTERPIECE *ONE HUNDRED YEARS OF SOLITUDE,* COLOMBIAN AUTHOR Gabriel García Márquez takes the reader to the mythical jungle village of Macondo, where, in one oft-recounted scene, residents suffer from a disease that causes them to lose all memory. The malady erases "the name and notion of things and finally the identity of people." The symptoms persist until a traveling gypsy turns up with a drink "of a gentle color" that returns them to health. In a 21st-century parallel to the townspeople of Macondo, a few hundred residents from Medellín, Colombia, and nearby coffee-growing areas have begun to assist in the search for something akin to a real-life version of the gypsy's concoction. Medellín and its environs are home to the world's largest contingent of individuals with a hereditary form of Alzheimer's disease. Members of 26 extended families, with more than 5,000 members, develop early-onset familial Alzheimer's, usually before the age of 50, if they harbor an aberrant version of a particular gene.

Familial Alzheimer's, passed down as a dominant genetic trait from only one parent, accounts for less than 1 percent of the more than 35 million cases of Alzheimer's and related dementias worldwide, but its hallmark brain lesions appear to be identical to those in the more common late-onset form of the disease, in which symptoms do not appear until after the age of 65.

The predictability of disease onset in the Medellín families has attracted the attention of a group of scientists and pharmaceutical companies who are considering a novel approach to research that will test drugs in patients before the first signs of dementia appear.

In recent years a number of drug candidates for treating mild or moderate Alzheimer's have failed, persuading researchers that much of the disease pathology—accretions of aberrant proteins and loss of brain cells or circuits—begins well before the memory loss becomes apparent. This growing realization, confirmed by new technologies that can track the disease years before the first symptoms, suggests that to be most successful, treatment must start during the many years when the insidious disease process is already under way, even though a patient's memory remains intact.

Consequently, a major thrust of much Alzheimer's research is shifting toward arresting the disease in advance of symptoms—not only with drugs but also with lifestyle measures that would be safer and less costly than filling a drug prescription for 10 or 20 years.

TODAY'S DRUGS

Some Relief, but Not Enough

Current drugs treat cognitive symptoms only, not the underlying disease process, and work for a limited time, from months to a few years.

Drug Class
Acetylcholinesterase inhibitor
(Examples: donepezil, galantamine)

What It Does
Blocks the action of an enzyme, acetylcholinesterase, thereby increasing levels of the brain chemical acetylcholine. Extra acetylcholine improves cognition, mood and behavior and so promotes better daily functioning.

Drug Class
NMDA receptor antagonist
(One drug: memantine)

What It Does
Helps to quell overactivity by a signaling chemical, glutamate, that can lead to the death of neurons. The drug does not interfere with the buildup of cell lesions that may drive progression of the disease.

AN EARLY START

THE COLOMBIAN ALZHEIMER'S FAMILIES stand in the vanguard of prevention research. Francisco Lopera, the neurologist who more than 30 years ago first came across the families who were later discovered to bear the *paisa* mutation (named after the moniker for the people of the region), has begun to contact hundreds of still healthy family members. He has recruited them to participate in a test of drugs that would remove or stop the buildup of toxic protein fragments, amyloid-beta peptides, that damage brain cells early in the disease process. "The contribution made by these families may shed a lot of light on the treatment and prevention of both early- and late-life Alzheimer's," Lopera says.

© 2015 Scientific American

In the $100-million clinical trial, which began treating patients in late 2013 and is part of a broader effort called the Alzheimer's Prevention Initiative (API), healthy, mutation-bearing family members around the age of 40 are receiving an antiamyloid drug called crenezumab, made by Genentech. Besides Genentech, the Banner Alzheimer's Institute in Phoenix is also playing a pivotal role—and the National Institutes of Health has made a major contribution to the funding. The trial in Colombia also complements a number of separate trials now starting up that are treating patients with drugs before symptoms begin.

The trial will evaluate whether a treatment can delay or stop the inexorable silent progression of the disease if administered seven years before the average age of diagnosis in family members who carry the gene. Beyond testing specific therapies, the designers of the Colombian trials also plan to see whether tracking of Alzheimer's-specific biomarkers can indicate whether an experimental treatment is working. (A biomarker is a measurable indicator—such as a concentration of a particular protein—that changes in concert with progression or regression of a disease.) A reliable set of biomarkers would allow drug researchers and clinicians caring for patients to evaluate the success of a therapy relatively quickly, by measuring changes in such silent benchmarks, instead of having to wait to assess overt symptoms. The API, under the aegis of Banner, is also undertaking a similar set of trials with a U.S.-based group made up of carriers of two copies of a gene variant, *APOE* e4, that increases susceptibility to Alzheimer's, although carriers are not guaranteed to get the disease.

The API would serve as a model for making biomarker-based Alzheimer's prevention trials commonplace. Proving that a drug prevents a disease takes much longer and costs much more than ascertaining whether it works in a patient who is already sick.

With a set of biomarkers in hand, a pharmaceutical company can test whether a drug changes levels of amyloid or another biomarker, in the same way that physicians test cholesterol levels as a gauge of whether a statin is helping to prevent heart disease. "We

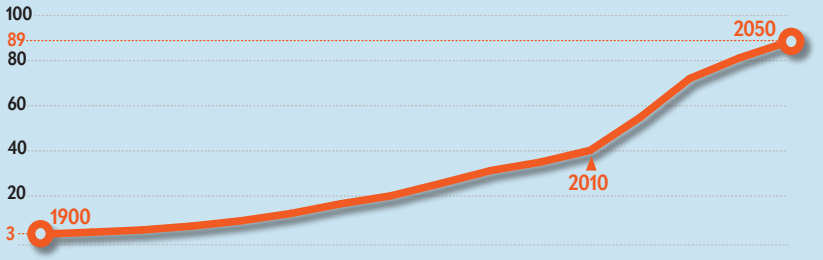
ALZHEIMER'S NUMBERS

The Coming Flood

As the U.S. population ages—along with that of the rest of the world—the number of new cases of Alzheimer's disease will soar because the incidence increases with age. In 2010 about 40 million people in the U.S. were senior citizens, a figure that will more than double to 89 million by 2050.

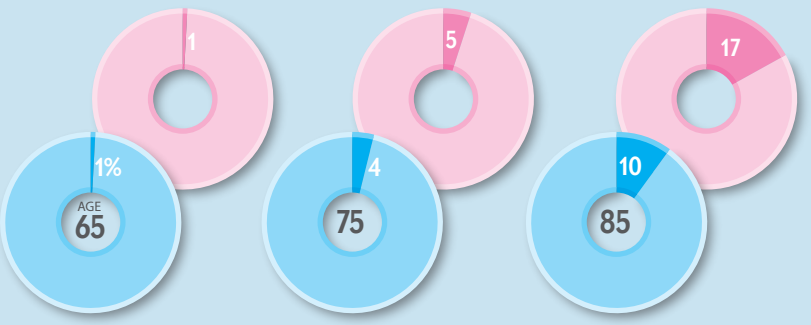
THE POPULATION IS AGING …

Millions of people aged 65 and older, living in the U.S.



… AND AGE IS THE BIGGEST RISK FACTOR FOR ALZHEIMER'S …

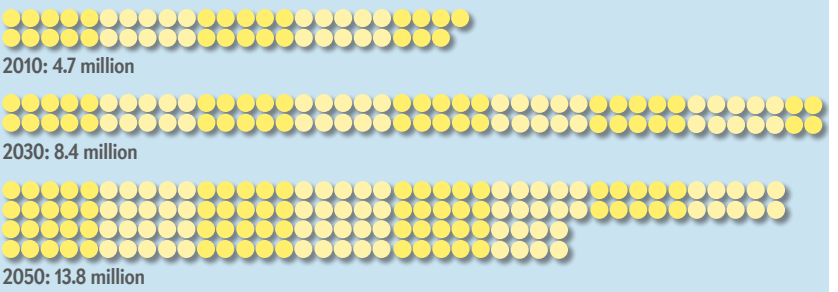
Risk of developing Alzheimer's at a given age over the next 10 years, for males and females



… SO THE NUMBER OF CASES IS GROWING

Numbers of people 65 and older in the U.S. with Alzheimer's will increase by more than 50 percent during the next 15 years

1 dot represents 100,000 people diagnosed with Alzheimer's



HOME VISIT with patient suffering from Alzheimer's disease.

LUCY READING-IKKANDA (*illustration*); DATA FROM U.S. CENSUS BUREAU (*top chart*); DATA FROM ALZHEIMER'S ASSOCIATION (*bottom two charts*); GETTY IMAGES (*photograph*)

© 2015 Scientific American

need to move presymptomatic treatments forward. Otherwise we could lose a whole generation," says Eric M. Reiman, executive director of the Banner Alzheimer's Institute, who, along with colleague Pierre N. Tariot, launched the API.

The challenges of prevention trials still loom large: the drawbacks posed by inevitable drug side effects are more difficult to weigh against potential benefits in patients who do not yet have symptoms. Moreover, no one can predict whether a drug that proves helpful for familial Alzheimer's will also work in patients who lack the particular gene mutation that brings on the early-onset form of the disease. But the urgency of finding new treatments—and the lure of a multibillion-dollar drug—has given momentum to prevention strategies. Given the wave after wave of drug failures, pharmaceutical companies have started to realize that clinical trials before symptoms appear may be the only way to find effective therapies.

Some treatments for Alzheimer's do exist, but they do little to delay disease progression. A true disease-modifying therapy would meet with overwhelming patient demand. Statisticians predict that by the middle of the century, the global prevalence of Alzheimer's will nearly quadruple, reaching 107 million. A treatment that delays disease onset by even five years would halve the number of people who die from the disease.

INSIDE YOUR HEAD

AN ALZHEIMER'S PREVENTION TRIAL based on biomarkers, dismissed as a fantasy a decade ago, may come to fruition because imaging and other technologies, now flourishing worldwide, can track biomarkers to reveal the nature of the underlying disease process. In the U.S. since 2004, the Alzheimer's Disease Neuroimaging Initiative (ADNI), a collaboration among pharmaceutical companies, academics and the National Institutes of Health, has been developing methods to better assess the effectiveness of drugs tested in individuals suffering from the disease, a goal that quickly expanded to look at what is happening during the time before an actual diagnosis is made.

One intriguing report of progress in the field came in 2010, when Clifford R. Jack, head of the group within ADNI studying biomarkers that can be detected with magnetic resonance imaging, described a model of how the disease likely progresses and paired it with biomarkers that seem able to track this pathology. Jack presented his work, which also appeared in a technical paper, to an online audience of more than 100 people during a Web seminar on Alzforum, a gathering that included many leading researchers in the field. Co-founded by June Kinoshita, a former *Scientific American* editor, Alzforum is a meeting place for the exchange of ideas, a repository of research information and a source of perhaps the most in-depth journalism anywhere on Alzheimer's research.

At the Web seminar, Jack noted that the biomarker measurements have demonstrated that the disease process begins years before the defining symptoms that allow a diagnosis to be made. During this time (estimated to range from five to 20 years), a particular type of amyloid peptide begins to aggregate outside of brain cells and damage synapses, the contact points between neurons. A radioac-

100 Years of Research

1906: German psychiatrist Alois Alzheimer first describes (based on a brain autopsy) the extracellular plaques and the tangles in neurons that characterize the disease.

Next 50 years: Memory loss and other symptoms are regarded as the senility that results from normal aging.

1960s: A link is established between cognitive decline and the number of plaques and tangles in the brain.

1980s: Researchers start to unravel the fundamental biochemistry that leads to plaques and tangles.

1990s: Several discoveries identify genetic factors underlying the disease, and the first drugs that improve symptoms come to market.

2000s: Imaging and spinal fluid samples enable scientists to track the disease course. A number of drugs that target disease processes fail in clinical trials, leading many to conclude that earlier treatment is needed.

PROGRESS TOWARD PREVENTION

New Tools Detect Silent Early Signs

Amyloid Accretion
5–20 years before diagnosis of Alzheimer's dementia

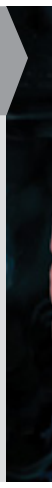
Early on, a protein fragment called amyloid-beta aggregates in the brain centers that form new memories. The amyloid buildup, a biomarker detected by the presence of plaques, results in damage to synapses, the interface between neurons (*detail*). Amyloid blocks chemical signals (neurotransmitters) from reaching receptors on receiving neurons. This buildup can be captured by various forms of neuroimaging, including positron-emission tomography (PET), that detect a radioactive compound, Pittsburgh imaging compound B (PIB), able to bind specifically to amyloid. A spinal tap can also be used to gauge the amyloid biomarker.

Tau Buildup
1–5 years before diagnosis

Before symptoms would justify an Alzheimer's diagnosis, a protein called tau inside neurons begins misbehaving. Normally tau helps to maintain the structure of tiny tubes (microtubules) critical to the proper functioning of neurons. But now phosphate groups begin to accumulate on tau proteins (*detail*), which detach from the microtubules. The tubules go on to disintegrate, and tau then aggregates, forming tangles that interfere with cellular functions. A sample of spinal fluid can detect this process.

Brain Shrinkage
1–3 years before diagnosis

As the underlying disease process advances, nerve cells start to die, and patients and family notice memory and other cognitive lapses. Cell death shrinks the brain in areas that involve memory (the hippocampus) and higher-level brain functions (the cortex) and thus can be tracked with a form of magnetic resonance imaging that measures brain volume. Such shrinkage accelerates and ultimately involves many areas of the brain.

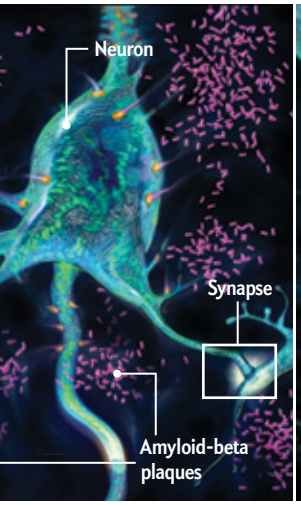


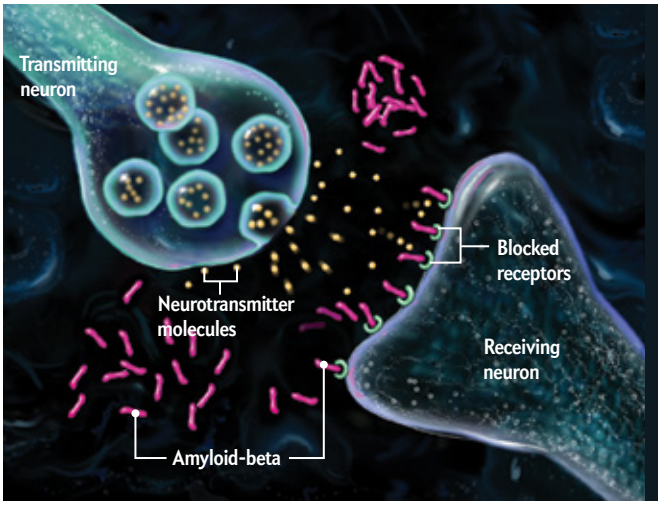
ANDREW SWIFT (*illustrations*)

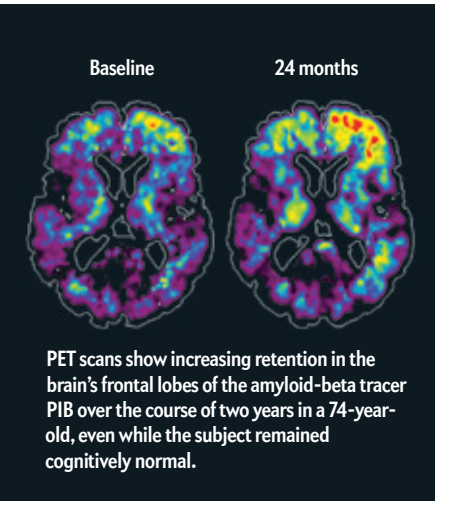
© 2015 Scientific American

The disease process underlying Alzheimer's (*below*) starts years before symptoms would lead to a diagnosis. Researchers can now track it in living patients with tools—including brain imaging and spinal fluid tests (*far right*)—that monitor Alzheimer's-related biomarkers: signs of biological changes (such as mounting levels of toxic proteins) that routinely occur in the course of the disease. Researchers hope that one day biomarker testing will identify incipient disease in people and that treatment in this early stage will delay or prevent dementia.

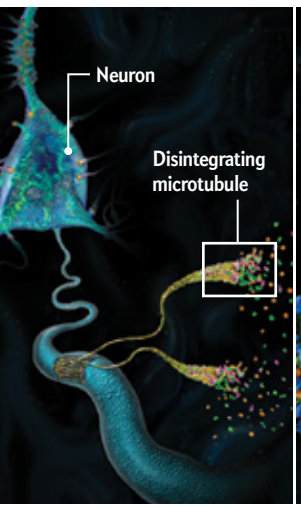
Biomarker Technologies

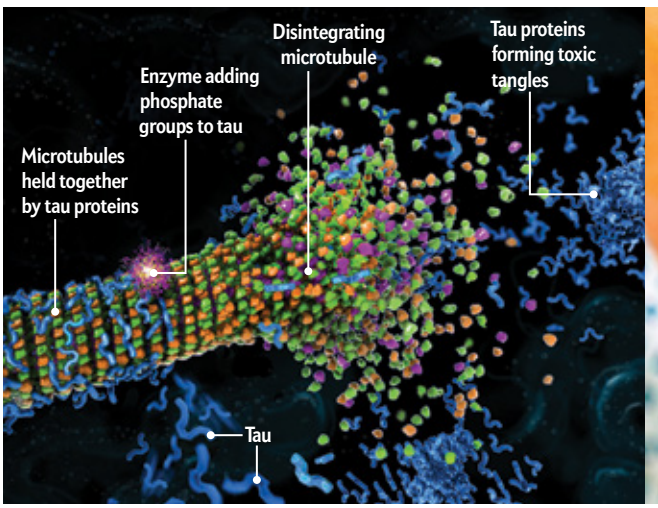


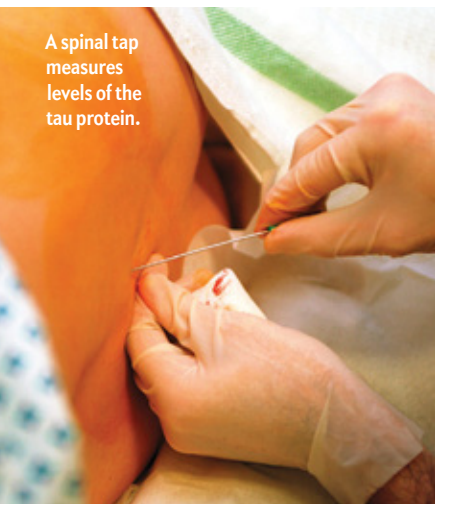


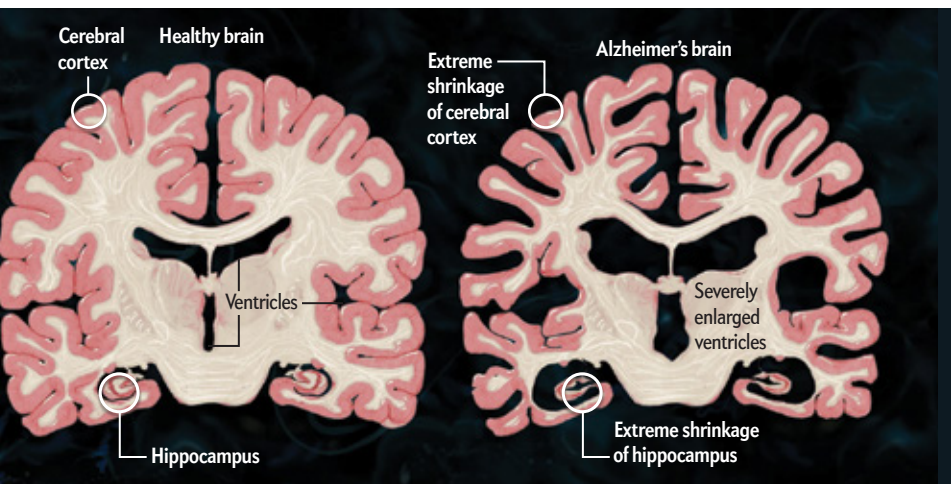


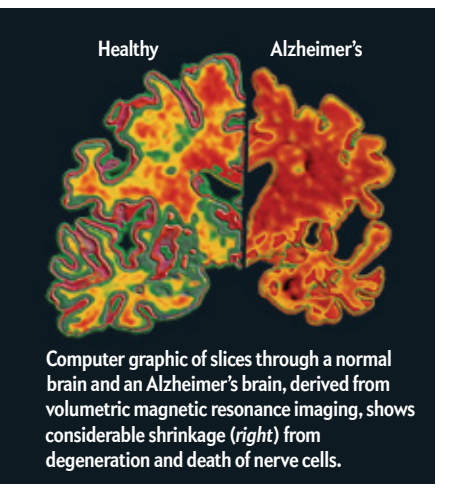
PET scans show increasing retention in the brain's frontal lobes of the amyloid-beta tracer PIB over the course of two years in a 74-year-old, even while the subject remained cognitively normal.




Disintegrating microtubule
Tau proteins forming toxic tangles
Enzyme adding phosphate groups to tau
Microtubules held together by tau proteins
Tau







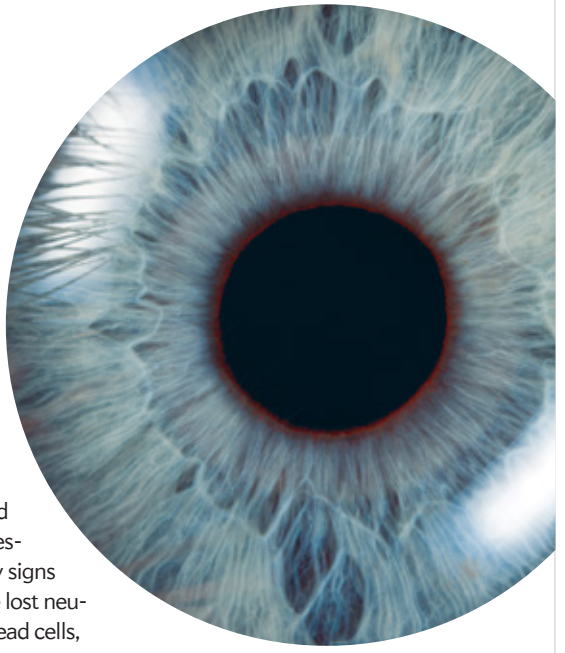
Computer graphic of slices through a normal brain and an Alzheimer's brain, derived from volumetric magnetic resonance imaging, shows considerable shrinkage (*right*) from degeneration and death of nerve cells.

COURTESY OF UNIVERSITY OF PITTSBURGH AMYLOID IMAGING GROUP (*PET*); DAVID HOFFMAN PHOTO LIBRARY *Alamy* (*spinal tap*); A. PAKIEKA *Photo Researchers, Inc.* (*brain comparison*); BASED ON A PRESENTATION BY CLIFFORD R. JACK *Mayo Clinic*

© 2015 Scientific American

Advance Warning

An eye-tracking test enters the running for a prognostic Alzheimer's screen



One in nine Americans aged 65 and older has Alzheimer's disease. Therapy could come in the form of new drugs, but some experts suspect drug trials have failed so far because compounds were tested too late in the disease's progression. By the time people show signs of dementia, their brains have lost neurons. No therapy can revive dead cells, and little can be done to create new ones.

So researchers running trials now seek participants who still pass as cognitively normal but are on the verge of decline. These "preclinical" Alzheimer's patients may represent a window of opportunity for therapeutic intervention. How to identify such individuals before they have symptoms presents a challenge, however.

Today most Alzheimer's patients are diagnosed after a detailed medical workup and extensive tests that gauge mental function. Other tests, such as spinal fluid analyses and positron-emission tomography (PET), can detect signs of approaching disease and help pinpoint the preclinical window but are cumbersome or costly. "There's no cheap, fast, noninvasive test that can identify people at risk of Alzheimer's," says Brad Dolin, chief technology officer of Neurotrack in Palo Alto, Calif., a company developing a computerized visual screening test for Alzheimer's.

Unlike other cognitive batteries, the Neurotrack test requires no language or motor skills. Participants view images on a monitor while a camera tracks their eye movements. The test draws on research by co-founder Stuart Zola of Emory University, who studies learning and memory in monkeys. When presented with a pair of images—one novel, the other familiar—primates fixate longer on the novel one. But if the hippocampus is damaged, as it is in people with Alzheimer's, the subject does not show a clear preference for the novel images.

The findings seem to hold in people. In a study published in 2013 Zola and his colleagues gave the half-hour test to 92 seniors. Scores predicted who would develop Alzheimer's three years in advance. The company has since developed a five-minute Web-based test that uses webcams and is launching a three-year study of the test with up to 3,000 seniors in Shanghai this winter. Additional studies in the U.S. will evaluate the tool alongside PET and other measures for preclinical Alzheimer's. And a number of pharmaceutical companies will include Neurotrack in clinical trials of Alzheimer's therapies in the next few years, according to Neurotrack's CEO Elli Kaplan. Experts not involved with Neurotrack think it shows promise. The test paradigm has "an excellent base of supporting literature," says Peter Snyder of Brown University.

Blood tests, retinal scans and computerized cognitive tests are also in the running as simple screens for presymptomatic Alzheimer's. It is unclear which is most accurate, and doctors likely would use several to assess the disease's progression. —*Esther Landhuis*

Esther Landhuis is a freelance science writer in the San Francisco Bay Area.

tive tracer molecule, such as Pittsburgh imaging compound B (PIB), can bind to amyloid in a patient's brain and then be imaged using positron-emission tomography (PET). The imaging technique, abbreviated PIB-PET, has shown that this aggregation process starts to level off before definitive symptoms arise.

Later on, but also before a diagnosis, a class of proteins called tau, which normally assist in providing structural support to neurons, become detached from the cells' scaffolding and clump into tangles, wreaking havoc inside the cells. The tau buildup can be detected by examining a sample of cerebrospinal fluid. This test can also look for decreasing levels of amyloid-beta, which occur as the peptides get removed from the fluid to form deposits in the brain. Together, decreasing levels of amyloid-beta and an increase in tau in the cerebrospinal fluid give a strong signal that the disease process is advancing.

Anywhere from one to four years before a person is diagnosed with Alzheimer's, a phase called mild cognitive impairment sets in. It is characterized by symptoms that range from memory lapses to poor decision making. Mild cognitive impairment can arise from causes other than Alzheimer's, but in those who are on the road to Alzheimer's dementia, mild cognitive impairment occurs because neurons in certain brain areas are damaged or dying—a loss that accelerates over time. (If memory problems are the primary symptom, the patient often progresses to Alzheimer's.) This stage can be tracked with a form of imaging called volumetric MRI, which measures shrinkage of the brain as neurons expire. The cascade of events, including the early accretion of amyloid, disrupts cell metabolism and can be monitored with a form of PET, fluorodeoxyglucose-PET (FDG-PET), that gauges the metabolic status of neurons.

BUT DOES THE PATIENT GET BETTER?

USING BIOMARKERS as the basis of clinical trials for prevention poses a set of challenges to both pharmaceutical companies and regulators—and constitutes a barrier to moving ahead with the API and other prevention efforts. To be approved, an Alzheimer's drug needs to show that it provides cognitive benefits for the patient

PETER A. KEMMER *Getty Images*

SECRETS OF STAYING YOUNG

© 2015 Scientific American

STATE OF THERAPY

Why Treatments Lag

Any drug that substantively delayed or stopped Alzheimer's would be an immediate blockbuster, perhaps exceeding sales for Prozac or Lipitor. No such drugs are on the market because investigators are still trying to understand how to alter the underlying mechanisms by which the disease causes dementia.

Drugs that impede amyloid buildup offer a case in point: a number of drug possibilities at various stages of testing can purportedly inhibit amyloid accumulation or foster its clearance. Yet several antiamyloid drugs tested in clinical trials have already failed. (The table at the right lists major classes of Alzheimer's drugs under development.) Some researchers wonder whether too little emphasis has been placed on interfering with other processes that contribute to the disorder. Among the 100 or so agents under development are prospective drugs that target the cell-damaging tau protein. Some are intended to quell inflammation, boost the functioning of mitochondria, enhance cerebral insulin levels or provide other protection for neurons. One high-profile failure involved Dimebon, a drug that did not target tau or amyloid. As with cancer and HIV, it may be necessary to combine several of these agents to slow or halt Alzheimer's. —*G.S.*

DRUGS UNDER STUDY	WHAT THEY DO
Inhibitors of enzymes that produce amyloid-beta	Such inhibitors block or modify the action of enzymes that cut a large protein (the amyloid precursor protein) in a way that releases the amyloid-beta peptides.
Vaccines or antibodies that clear amyloid-beta	Vaccines induce the body to produce antibodies that bind to amyloid and clear them from the brain. Unfortunately, in clinical trials, both vaccines and antibodies have induced side effects of varying severity in some patients.
Amyloid-beta aggregation blockers	Agents that prevent amyloid fragments from clumping could prevent damage to neurons.
Antitau compounds	These agents, though fewer in number than those that target the amyloid pathway, take various approaches, such as blocking production of the toxic form of the tau protein or impeding its aggregation into tangles.
Neuroprotective agents	Different strategies attempt to boost natural brain chemicals that enhance the health of neurons. In one, a gene is delivered into the brain to start production of a protective substance.

(in memory, language or a related measure) better than a placebo does.

If a biomarker is tracked instead of symptoms in a prevention study, researchers need to be sure that the measurements truly presage whether a subject is likely to develop dementia. For instance, investigators do not yet know whether changing amyloid-beta levels will ultimately prevent dementia, despite the large body of evidence suggesting that amyloid-beta contributes to disease development.

In fact, in one early trial of an amyloid therapy, the levels of the peptide decreased in some patients, but there was almost no evidence that cognition improved. "We're concerned that we might have a drug that affects a marker in the way that we predict but that it doesn't affect patients' clinical picture," says Russell Katz, former director of the division of neurology products for the Food and Drug Administration. "In other words, their disease continues to progress, and they don't get any better." Katz says a better approach to incorporating biomarkers in clinical trials would be to first show that reducing levels of amyloid or another biomarker benefits patients who have mild cognitive impairment or who are newly diagnosed with Alzheimer's and to attempt to use biomarkers in people without symptoms only afterward. "The best way to get there in my opinion is to start with patients who have symptoms, maybe very, very early on, and then work backward," Katz says.

But the researchers in the Colombian prevention trials assert that they may already be capable of using biomarkers to detect subtle changes in memory, thereby allaying Katz's concern. And Reiman cites work from his group that might offer another way to help ease regulator concerns. In that study, carriers of the *APOE* e4 gene variant showed a small decline in scores for memory on psychological tests many years before any cognitive deficit became noticeable. This level of sensitivity, Reiman says, means that applying a cognitive test along with a biomarker measure in a prevention trial might suffice to indicate, say, whether prospects for avoiding dementia really do improve as amyloid levels drop.

Some companies are already trying to gain a better understanding of how to use biomarkers. The ability to target only the patients who are more likely to get a diagnosis of Alzheimer's could facilitate assessment of whether the drug really works, results that would be less clear if the trial had included participants who have little chance of getting the disease. As prevention research grows in sophistication, interventions could begin even earlier, at the first appearance of the pathological proteins that signal the start of the relentless progression toward an eventual diagnosis of dementia. SA

Gary Stix is a senior editor at *Scientific American*.

MORE TO EXPLORE

The Alzheimer's Project: Momentum in Science. Based on the HBO documentary. John Hoffman and Susan Froemke, with Susan K. Golant. Public Affairs Books, New York, 2009.

The Alzheimer's Solution: How Today's Care Is Failing Millions and How We Can Do Better. Kenneth S. Kosik and Ellen Clegg. Prometheus Books, 2010.

Gabrielle Strobel of Alzforum led a discussion in 2010 about disease-tracking "biomarkers" with a number of leading researchers: www.alzforum.org/res/for/journal/detail.asp?liveID=179

© 2015 Scientific American

DIAGNOSIS

SCANNING FOR ALZHEIMER'S

A new test can identify the disorder's early stages. How will it help patients?

By Ingfei Chen

THE WAY DOCTORS DIAGNOSE ALZHEIMER'S DISEASE MAY BE starting to change. Traditionally clinicians have relied on tests of memory and reasoning skills and reports of social withdrawal to identify patients with Alzheimer's. Such assessments can, in expert hands, be fairly conclusive—but they are not infallible. Around one in five people who are told they have the neurodegenerative disorder actually have other forms of dementia or, sometimes, another problem altogether, such as depression. To know for certain that someone has Alzheimer's, doctors must remove small pieces of the brain, examine the cells under a microscope and count the number of protein clumps called amyloid plaques. An unusually high number of plaques is a key indicator of Alzheimer's. Because such a procedure risks further impairing a patient's mental abilities, it is almost always performed posthumously.

In the past 10 years or so, however, scientists have developed sophisticated brain scans that can estimate the amount of plaque in the brain while people are still alive. In the laboratory, these scans have been very useful in studying the earliest stages of Alzheimer's, before overt symptoms appear. The results are reliable enough that in 2012 the Food and Drug Administration approved one such test called Amyvid to help evaluate patients with memory deficits or other cognitive difficulties.

Despite the FDA's approval, lingering doubts about the exact role of amyloid in Alzheimer's and ambivalence about the practical value of information provided by the scan have fueled debate about when to order an Amyvid test. Not everyone who has an excessive amount of plaque develops Alzheimer's, and there is generally no way to predict whom the unlucky ones will be. Recent studies have shown that roughly one third of older citizens in good mental health have moderate to high levels of plaque, with no noticeable ill effects. And raising the specter of the disorder in the absence of symptoms may upset more people than it helps because no effective treatments exist.

A national clinical trial, known as the A4 Study, is investigating whether giving an experimental drug as soon as the scans de-

Illustration by Davide Bonazzi

© 2015 Scientific American

tect the formation of plaques can slow or halt the development of Alzheimer's. Even if the results are encouraging, a new drug will take many years to reach the market, and doctors must decide how to use scans responsibly in the meantime. "The whole field is grappling with this," says neurologist Reisa Sperling of Brigham and Women's Hospital. She thinks the scan could bring clarity to challenging diagnoses, but "as a predictive test, it's not ready."

TELLTALE TROUBLE

SCIENTISTS FIRST LINKED amyloid plaques to what is now called Alzheimer's disease more than 100 years ago. In 1906 German psychiatrist Alois Alzheimer documented unusual protein knots in the brain of a deceased dementia patient. By the mid-1980s scientists determined that such plaques are made up of a protein they named amyloid-beta.

Healthy neurons produce plenty of amyloid-beta, but its precise purpose remains a mystery. In the initial stages of Alzheimer's and other neurodegenerative disorders, the proteins begin to behave strangely, sticking together to form larger and larger clumps. Scientists are still unsure whether the resulting plaques are primarily responsible for the devastating loss of millions of neurons that characterizes Alzheimer's or whether they are, instead, a by-product of some other, as yet undetermined, cause.

Nevertheless, the clumps form long before any explicit signs of dementia, and numerous plaques remain one of the best indicators of the disorder. Neurologists John C. Morris, Randall Bateman and their colleagues at Washington University in St. Louis have been tracking the health of people with a rare genetic mutation that guarantees Alzheimer's will strike them at a young age. They have detected amyloid plaques in the brain 15 years before cognitive problems typically appear in such individuals.

Attempts to design a scan that could spot amyloid first began more than a dozen years ago at the University of Pittsburgh. Researchers injected patients with a small, benign amount of a radioactive dye they named Pittsburgh imaging compound B, or PIB. The dye traveled through the blood to the brain and clung exclusively to clusters of amyloid protein. Scanning the brain with a positron-emission tomography (PET) machine then produced images that highlighted any plaques by detecting radiation in the form of gamma rays emanating from the dye.

Scientists at Philadelphia-based Avid Radiopharmaceuticals built on the Pittsburgh approach by developing Amyvid, a longer-lasting dye that gave clinicians more time to scan their patients. Eli Lilly bought the company in 2010 for $300 million. Two years later the FDA approved the Amyvid test, which about 450 imaging centers in the U.S. now offer, usually for $3,000 or more. (Similar tests, Vizamyl and Neuraceq, won approval more recently.)

TO SCAN OR NOT TO SCAN

TOGETHER THE FDA and the neurological community have approached Amyvid with a mix of enthusiasm and trepidation. Officially the test's primary purpose is to exclude an Alzheimer's diagnosis in someone who already has cognitive impairment, which is particularly helpful when the causes are unclear. An expert task force convened by the Alzheimer's Association and the Society of Nuclear Medicine and Molecular Imaging published guidelines in 2013 that advised limiting the test's use to patients with unexplained, persisting mild cognitive impairment (MCI) and to those who either have developed dementia unusually early or have dementia with atypical symptoms, such as hallucinations or delirium. Determining whether Alzheimer's is the culprit in such cases has always been difficult, and an amyloid scan is exactly the kind of tool that can provide some valuable assistance. If a scan finds few plaques, physicians can more confidently rule out Alzheimer's and explore other explanations, such as a rare degeneration of the brain's frontal lobes.

The task force also advised against amyloid scans for people with no cognitive impairment. Panelists worried not only that amyloid-positive results might send some vulnerable individuals spiraling into depression or perhaps even suicide but also that the information may make it harder for them to get long-term care insurance or renew a driver's license, says task force member Jason Karlawish, a professor of medicine and medical ethics at the University of Pennsylvania.

Despite these cautious guidelines, which Eli Lilly supports, many people in the medical community have reservations. Task force member and neurologist Norman Foster of the University of Utah worries that some doctors and patients will rely on amyloid scans as a diagnostic shortcut in lieu of a more thorough evaluation that includes memory and reasoning tests. And given the lack of effective treatment, a scan suggesting that someone with mild cognitive impairment has early Alzheimer's may yield more anxiety than practical guidance. "What do you do with that information?" asks neuroscientist William Jagust of the University of California, Berkeley.

Some experts say that the scans are beneficial if they help patients prepare for the changes in health and lifestyle that come with Alzheimer's. Others argue that the test is not meaningful if it does not alter how a patient is treated. The federal agency that oversees Medicare insurance took the latter view in September 2013, when, because of insufficient evidence that the scan improves patient health, it declined to cover Amyvid for now except in certain clinical trials. Avid's CEO Daniel Skovronsky acknowledges that figuring out how best to use the new technology will take considerable time and debate. In the meantime, though, Avid's parent company Eli Lilly is funding a lawsuit by three elderly women who are pressing for Medicare to cover Amyvid testing.

The nationwide A4 Study, which began in early 2014, could strengthen the case for amyloid imaging if its outcomes are auspicious. In that trial, Sperling, Karlawish and investigators at 60 U.S. and Canadian medical centers aim to scan 3,000 healthy senior citizens to identify 1,000 amyloid-positive individuals who will receive either a drug called solanezumab or a placebo for three years.

Before anybody slides into a PET scanner, however, participants are prescreened for mood, depression and anxiety to ensure they are capable of "handling uncertainty and, potentially, what could be construed as bad news if they learn that they are amyloid-positive on imaging," Karlawish says. "There will be some people who are not, frankly, allowed to go forward."

The trial's results are not expected until 2019. But with any luck, they will confirm that solanezumab could become a viable treatment in the future, as well as help doctors decide whether it makes sense to get an early look at Alzheimer's today. SA

Ingfei Chen is a freelance journalist in California. She has written for the *New York Times* and the Food & Environment Reporting Network.

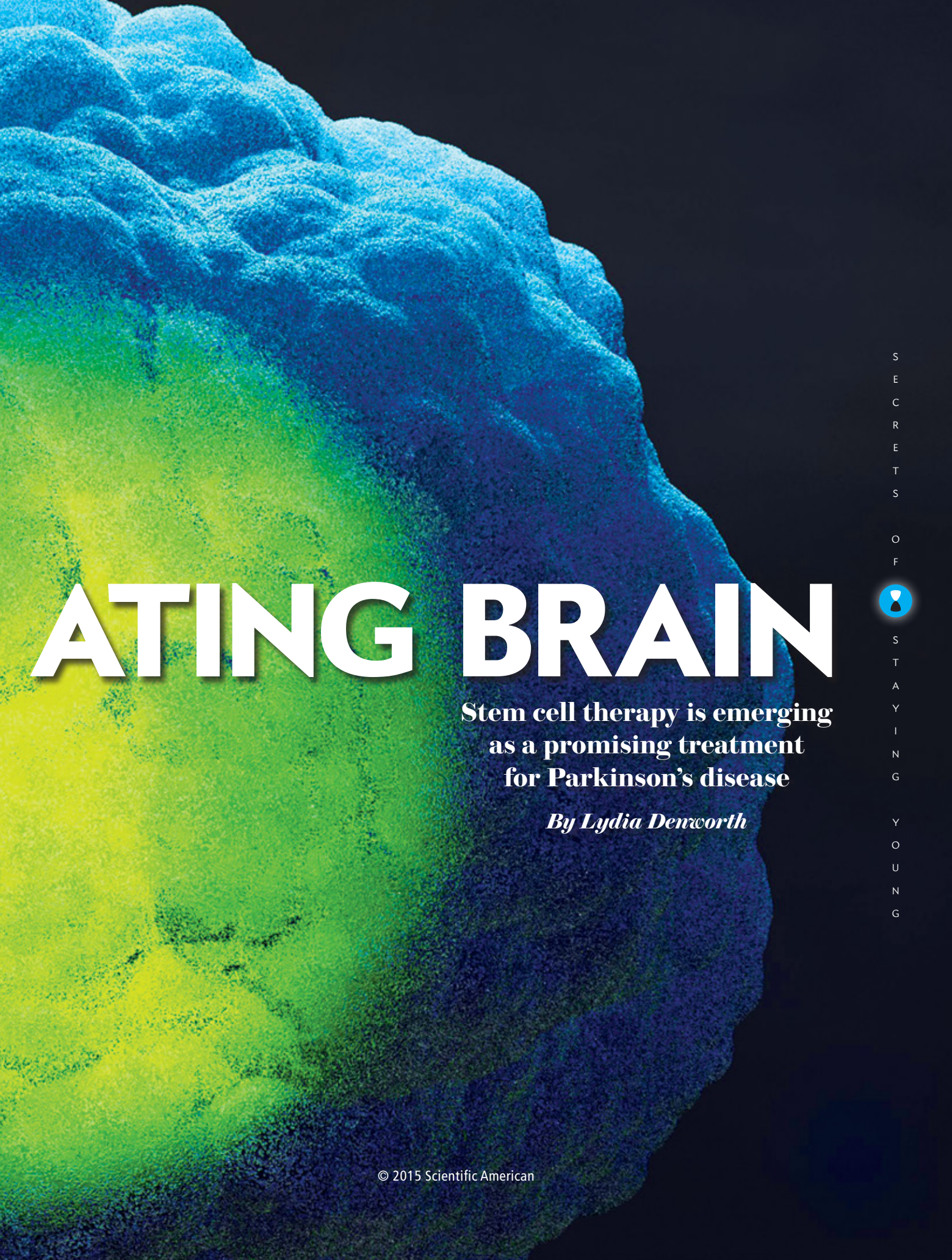
© 2015 Scientific American

REGENERATIVE MEDICINE

THE REGENER

This stem cell sports a glowing green nucleus.

© 2015 Scientific American



SECRETS OF STAYING YOUNG

ATING BRAIN

Stem cell therapy is emerging as a promising treatment for Parkinson's disease

By Lydia Denworth

© 2015 Scientific American

NEUROSURGEON IVAR MENDEZ OF THE UNIVERSITY OF SASKATCHEWAN OFTEN SHOWS a video clip to demonstrate his work treating Parkinson's disease. It features a middle-aged man with this caption: "Off medications." The man's face has the dull stare typical of Parkinson's. Asked to lift each hand and open and close his fingers, he barely manages. He tries but fails to get up from a chair without using his hands. When he walks, it is with the slow, shuffling gait that is another hallmark of Parkinson's, a progressive neurological disorder that afflicts an estimated one million Americans, most of them older than 60.

Then the video jumps forward in time. The same man appears, still off medications. It is now eight years since Mendez transplanted dopamine cells from a fetus into the patient's brain. These neurons, which live in a midbrain region called the substantia nigra and secrete the neurotransmitter dopamine to initiate movement, are the ones that die off in Parkinson's. The man has aged, but his energy and demeanor are characteristic of a much younger man. Asked to do the same tasks, he smoothly raises his arms high and flicks his fingers open and shut rapidly. Arms crossed on his chest, he rises from a chair with apparent ease. Then he struts down the hall.

In the 25 years since the first few patients received transplants as part of a clinical trial at University Hospital in Lund, Sweden, hopes of using cell-based therapy as a treatment for Parkinson's have repeatedly risen and then been dashed. Stem cells are a biological raw material of enormous potential because they can generate new cells through the ability to divide indefinitely and to give rise to specialized cells. These cells can then be used to repair brain damage from degenerative disorders such as Parkinson's. Stem cells, however, have been hard to come by. So far the cells transplanted in humans have been derived from aborted fetal tissue, although scientists have also transplanted stem cells derived from human embryos and adult skin cells into animals. Thorny political and ethical issues limit access to both fetal cells and embryonic stem cells, and fetal cells are in particularly short supply. Two large clinical trials using fetal tissue, published in 2001 and 2003, were considered failures because of their widely variable results; not enough pa-

IN BRIEF

Stem cells derived from aborted fetal tissue can divide indefinitely and give rise to specialized cells, which can be used to repair brain damage from degenerative disorders such as Parkinson's.

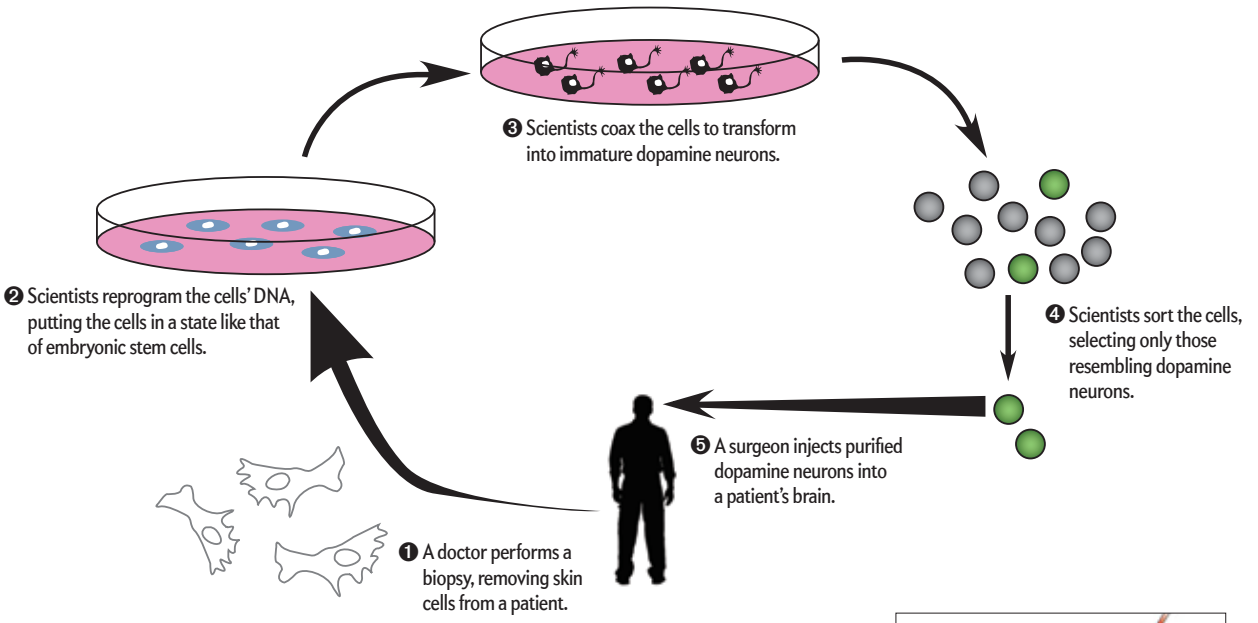
Ethical concerns, limited access to stem cells and mixed results from clinical trials have stifled progress in advancing stem cell therapies for degenerative disorders; however, novel techniques for producing and transplanting these cells have inspired optimism.

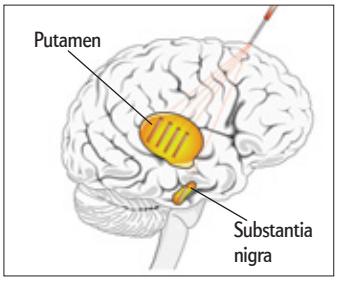
Researchers are aiming to use stem cells to treat more than a dozen diseases, including diabetes, spinal cord injury and several forms of cancer.

PRECEDING PAGES: DAVID MACK *Science Source*

© 2015 Scientific American

Replacing Lost Neurons


❸ Scientists coax the cells to transform into immature dopamine neurons.
❷ Scientists reprogram the cells' DNA, putting the cells in a state like that of embryonic stem cells.
❹ Scientists sort the cells, selecting only those resembling dopamine neurons.
❺ A surgeon injects purified dopamine neurons into a patient's brain.
❶ A doctor performs a biopsy, removing skin cells from a patient.



Scientists can create stem cells from an adult's own tissues, producing a limitless supply. After extracting the cells—say, through a skin biopsy—researchers chemically coax them to revert to an embryonic state. They can then be transformed into dopamine neurons (or potentially other types of cells), which can be transplanted into the brain. To treat Parkinson's disease, one strategy involves injecting immature dopamine neurons through the skull into the putamen and the substantia nigra (*right*). So far all patients have been treated with cells derived from fetal tissue; none have received reprogrammed adult cells.

tients improved by the study end points, and some developed serious side effects. Many scientists gave up on cell therapy.

But a handful of laboratories persevered. Now new evidence showing that transplantation can work well, as in Mendez's patient, and possible new sources of cells free of ethical concerns have sparked a fresh optimism. This year neurologist Roger A. Barker of the University of Cambridge plans to lead the first large clinical trial of cell therapy for Parkinson's in a decade. "We've broken through the old barriers," says cell biologist Ole Isacson of Harvard University.

The momentum most likely will propel cell therapies for other disorders as well. Researchers are trying to apply the technique to more than a dozen diseases, including diabetes, spinal cord injury and several forms of cancer [see "Stem Cell Repair Shop," on page 81]. In addition to Parkinson's, the most significant progress has been made with retinal diseases. Clinical trials are under way to use retinal pigment epithelial cells for treatment of macular degeneration. According to the California Institute for Regenerative Medicine, theoretically there is no disease to which stem cell therapy could not be applied. In each case, the requirements depend on the difficulties inherent in generating the specific type of cell scientists hope to replace.

Progress in Parkinson's has been particularly promising, Isacson says, because "it's easier to solve." The debilitating movement difficulties characteristic of the disease have a relatively straightforward cause: dopamine loss. And researchers were able to generate dopamine neurons from stem cells quite quickly. Cell therapy typically leads to restored mobility and function—improving patients' gait, for instance, and reducing tremor—but does not ameliorate every aspect of Parkinson's. Patients may still suffer from dementia, gastrointestinal problems and sleep disorders, for instance. Yet in the best-case scenario, patients could gain 20 to 30 years of excellent quality of life with a single intervention and require virtually no medications. "You've not cured the disease," Barker says, "but you've transformed the natural history of Parkinson's disease."

DELIVERING DOPAMINE

A MILD TREMOR in the hand or some other extremity is often the first sign of Parkinson's. Tremors are followed by rigidity in the muscles, a stooped posture and the distinctive difficulty walking first described by James Parkinson in 1817. The movement difficulties relate to the loss of a dopamine neuron called A9 in the substantia nigra, which among other things controls the initia-

SCIENTIFIC AMERICAN MIND; SOURCE: IVAR MENDEZ *University of Saskatchewan* AND OLE ISACSON *Harvard University*; ISTOCKPHOTO (*man*); IVAR MENDEZ (*brain inset*)

© 2015 Scientific American

tion of motion. By the time the first tremor appears, patients have already lost about 70 percent of those A9 neurons—a threshold that is like a water level, Isacson says. They hit the water and begin to sink under a flood of movement troubles.

Since the 1960s Parkinson's has been treated with medications that replace missing dopamine in the brain. L-Dopa is a dopamine precursor, and doses of this small molecule cross the blood-brain barrier and enter brain cells, which convert L-Dopa into dopamine and release it. Other drugs, known as dopamine agonists, stimulate dopamine receptors in the absence of the neurotransmitter, thereby mimicking its effects. The medications improve parkinsonian symptoms, but their benefits diminish over time, and they carry side effects such as alternating periods of mobility and immobility and the emergence of additional jerky movements.

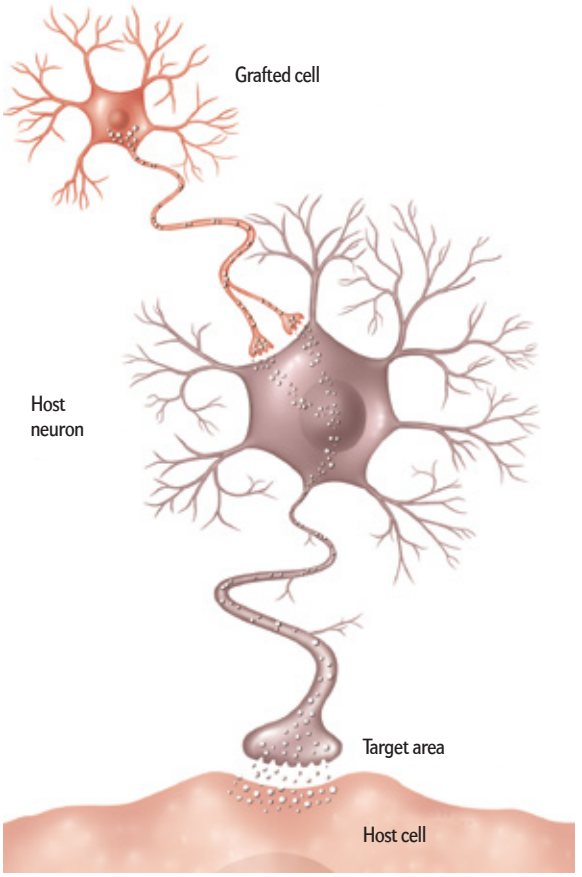
In the 1990s clinicians developed an alternative therapy called deep-brain stimulation (DBS), the surgical insertion of an electrode that delivers electrical pulses to directly alter neuronal activity in a specific area of the brain. The treatment can work well. At the University of California, San Francisco, Medical Center, for example, 45 to 70 percent of patients who receive DBS for Parkinson's improve. Yet over time, patients begin to decline again because the electrode stimulation can no longer compensate for the continuing loss of dopamine. Cell-based therapy, in contrast, is designed to directly restore the cells lost in the disease process.

The earlier large clinical trials of cell therapy suffered from multiple problems. For example, it now appears that some of the patients selected were too old and their disease too advanced to get good results. Instead of infusing a substance containing a single type of cell, surgeons transplanted chunks of tissue, which included other material that triggered immune reactions. The procedure itself was conducted differently by every team. Moreover, the end points for the studies were too short—neither was more than two years—for the transplanted cells to take full effect.

Of the patients who have received cell-based therapy for Parkinson's, those transplanted by Mendez's team have done best. Mendez began transplanting fetal cells into patients in the late 1990s, when he was at Dalhousie University in Nova Scotia. He improved the preparation of the cells by treating them to encourage growth and creating pure cell suspensions instead of transplanting chunks of tissue. Using a computerized injector that he developed to standardize the process, Mendez targeted two brain areas instead of one—the substantia nigra, where dopamine cells naturally originate, and the putamen, which their axons need to reach. All 10 of his patients improved significantly on the standard Parkinson's rating scale, which measures the course of the disease. In a separate postmortem analysis of five patients published in 2008, Mendez and Isacson, who have been collaborating for about 10 years, found that the grafted neurons survived without signs of degeneration for as long as 14 years. "Methods matter," Mendez says. "We now have all the experience and the techniques and the instruments that will be able to plant these cells safely into the human brain."

RESTORATION

When a neuron (*red*) derived from a stem cell is injected into the brain, the cell grows and connects with existing neurons (*purple*). The ability of cell transplants to integrate with established brain circuitry is essential to restoring function.



NEW KINDS OF CELLS

THE BIGGEST REMAINING CHALLENGE is obtaining enough viable stem cells. The fetal cells implanted to date have been harvested from the midbrain of an aborted fetus aged six to nine weeks. Such stem cells have already differentiated into dopamine neurons yet retain the capacity to generate more new neurons after transplantation. Still, fetal cells "are not the answer," Mendez acknowledges. Politics aside, there will never be enough for all the patients who would need them.

Another possibility emerged in 1998, when cell biologist James A. Thomson of the University of Wisconsin–Madison and his colleagues derived the first embryonic stem cell line. They were working with the blastocyst of a human embryo, a brief early developmental stage when the ball of cells contains an in-

STILL, FETAL CELLS "ARE NOT THE ANSWER," ONE NEUROSURGEON SAYS. POLITICS ASIDE, THERE WILL NEVER BE ENOUGH FOR ALL THE PATIENTS WHO WOULD NEED THEM.

IVAR MENDEZ *University of Saskatchewan*

© 2015 Scientific American

Stem Cell Repair Shop

For decades researchers have explored the use of cells as a tool for treating a wide range of disorders. Despite its promise, stem cell repair of the body remains experimental. The following is a snapshot of progress in bringing such therapy into practice for five pressing medical conditions. *—Roni Jacobson*

Condition	Pathology	Hypothesis	Research Stage
Amyotrophic lateral sclerosis (ALS)/ Lou Gehrig's disease	Cells in the brain and spinal cord that control movement die off, leading to paralysis	Transforming stem cells into new neural support cells could protect motor neurons from further destruction	Preliminary trials in humans have determined that the intervention is safe, and researchers have begun testing whether it can slow decline or improve symptoms
Brain cancer	A type of brain tumor called a high-grade glioma is hard to treat because the blood-brain barrier prevents cancer drugs from reaching it	Neural stem cells could home in on the malignant brain cells to deliver cancer-killing agents without damaging healthy tissue	Safety trials in humans began in 2010. So far researchers have seen no adverse effects and hope to begin trials next year to establish the optimal dose
Multiple sclerosis	Inflammation in the brain and spinal cord damages myelin, a material that surrounds nerve cells and enables them to transmit signals effectively	Stem cells harvested from a patient's own bone marrow could be used to generate a whole new immune system; alternatively, engineered cells could replenish myelin	Results are encouraging: In a 2014 NIH-sponsored study, regenerating the immune system from stem cells caused most of the 25 patients to go into remission for at least three years
Spinal cord injury	Nerve fibers in the brain and spinal cord are damaged or severed, leading to complete or partial paralysis	Stem cells could scaffold, and potentially bridge, damaged and severed nerve fibers, although extensive scar tissue might impede regeneration	Researchers are recruiting patients for a safety trial to be completed in 2016
Type 1 diabetes	The body's immune system attacks and destroys the cells in the pancreas that produce insulin	Embryonic stem cells that mature into insulin-producing cells could replace missing pancreatic tissue	In 2012 researchers reported curing diabetes in mice using a stem cell method. They are applying to the FDA to start human trials

Roni Jacobson is a freelance science journalist based in Brooklyn, N.Y.

ner clump of 20 to 30 cells that are capable of growing into any of the more than 200 types of adult cells in the body. Unlike fetal tissue cells that have started down the path to differentiation, these so-called pluripotent stem cells have the potential to produce any type of tissue in the body.

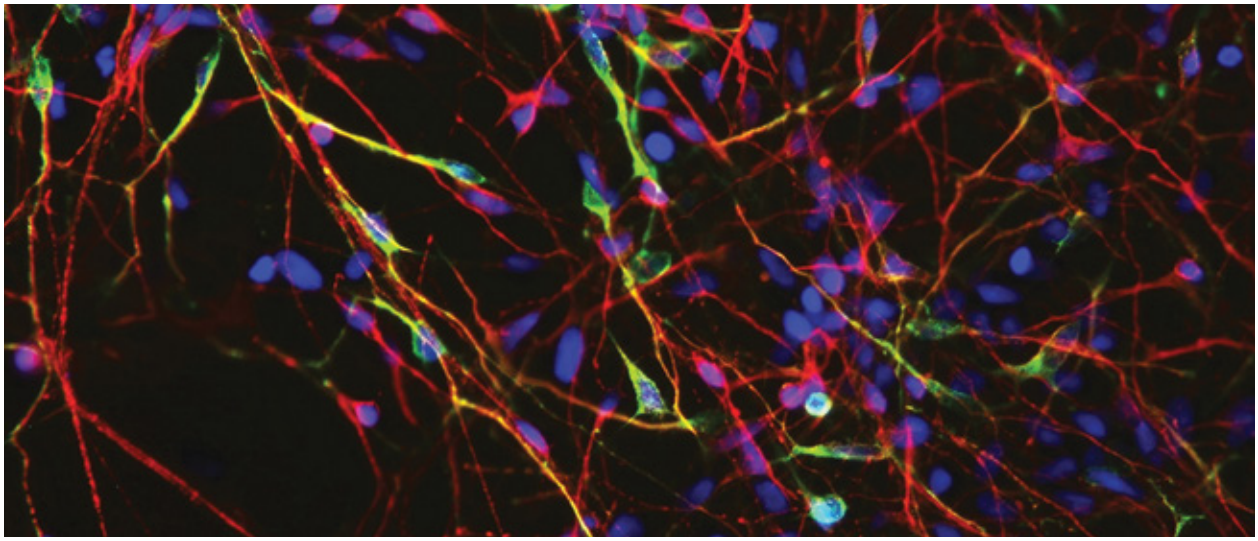
Thomson's team removed those cells and nurtured them in the lab so that they divided. The result was an infinitely renewable lab-maintained source of stem cells—a cell line—that would not require further new embryos. The ethics were still complicated by the original use of embryos, but suddenly large-scale cell-based therapy seemed achievable. The challenge was to coax those embryonic stem cells to develop into the specific cells needed to treat a disease—dopamine neurons for Parkinson's, for instance, or insulin-producing cells for diabetes.

Also in 1998 Isacson's group reported that it had done just that in mice. The researchers differentiated A9 neurons from mouse blastocysts. When they injected those A9 cells into a mouse brain, they found that the cells lived and formed connec-

© 2015 Scientific American

NEW NEURONS

Some of these neurons, derived from human embryonic stem cells, have become functional dopamine-synthesizing neurons (*yellow*), giving researchers hope that they could serve as replacements for defective neurons in the brain of people with Parkinson's.



tions with the other neurons in the brain. In 2002 Isacson's group showed that the same procedure restored movement and mobility in a rat with a drug-induced version of Parkinson's. Several other groups achieved similar recovery in rodents. Immediately researchers tried to create A9 neurons from human embryonic stem cells—but that step proved more difficult. "For nearly 10 years that was largely a failure," says cell biologist Lorenz Studer of the Memorial Sloan Kettering Cancer Center. "We would have expected the cells to behave well, but they did not."

A breakthrough with an alternative approach came in 2007, when the team of biologist Shinya Yamanaka of Kyoto University in Japan figured out how to create stem cells from an adult's own tissues. Beginning with adult mouse skin cells, Yamanaka's team "reprogrammed" the cells biochemically, driving them back to something resembling an embryonic stem cell, which could then be used as a basis for deriving a totally different kind of body cell, such as a neuron.

In essence, Yamanaka's group had found a way to create a limitless supply of stem cells from adult skin cells, thereby sidestepping the political and ethical issues that surround research with embryos. The accomplishment won Yamanaka the 2012 Nobel Prize in Physiology or Medicine. Furthermore, if the cells, which are called induced pluripotent stem cells, always originate with the individual patient being treated, the considerable risk of immune rejection would disappear. "They solved a very big problem," says Mahendra Rao, former director of the National Institutes of Health's Center for Regenerative Medicine and now vice president of regenerative medicine at the New York Stem Cell Foundation.

NEWLY NIMBLE MONKEYS

A YEAR AFTER YAMANAKA'S DISCOVERY, Isacson's team showed that it could create A9 dopamine neurons from such reprogrammed adult rodent cells. The scientists soon began putting the new cells in mice and rats with signs of Parkinson's, and in 2008 they reported improved function. Then they turned to nonhuman primates. Working with a monkey with drug-induced Parkinson's, Isacson's group harvested the monkey's skin cells, drove them back to an embryonic state, then differentiated them into dopamine neurons and put them into the monkey's brain. For two years, they monitored the monkey. In results presented at conferences late in 2013, they showed that according to positron-emission tomography (PET) scans the grafted dopamine neurons had survived and grown. About eight months after the transplant, the monkey's motor disorder ceased. A postmortem analysis showed that the new neurons had made connections with other neurons throughout the brain area where they had been grafted.

The same year two other groups also reported success with adult-derived stem cells and monkeys, including the lab of cell biologist Su-Chun Zhang of the University of Wisconsin–Madison and Yamanaka and his colleague Jun Takahashi. "All three groups now demonstrate pretty unequivocally that the graft can survive, can differentiate into the right type of cells and

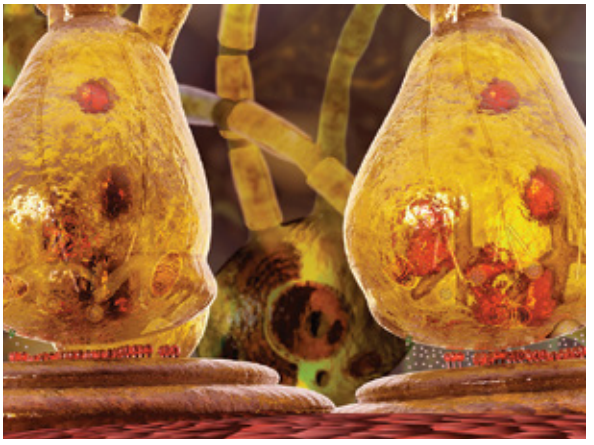
THE GRAFTED NEURONS HAD SURVIVED AND GROWN IN THE MONKEY'S BRAIN. ABOUT EIGHT MONTHS AFTER THE TRANSPLANT, THE MONKEY'S MOTOR DISORDER CEASED.

SCIENCE SOURCE

© 2015 Scientific American

DOPAMINE DEFICIT

In Parkinson's, neurons that release the neurotransmitter dopamine (*digital illustration below, right*) produce less dopamine as they sicken (*left*) and eventually die. After a patient loses about 70 percent of one type of dopamine neuron, movement problems appear.



CAROL AND MIKE WERNER *Science Source*

then can integrate into the brain structurally," Zhang says.

Isacson's monkey is the only one to be observed for a longer period—two years—and to have shown functional recovery. The researchers are pursuing longer-term studies with more monkeys to convincingly show both safety and efficacy. Clinical trials could follow, possibly within a few years, say Mendez and Isacson, who are convinced that these adult-derived cells are the future.

Others are still betting on embryonic stem cells. In 2011 and 2012 Studer's lab and that of neurobiologist Malin Parmar of Lund University successfully differentiated human embryonic stem cells into dopamine neurons. When grafted into a mouse, rat or monkey with parkinsonian symptoms, these cells survive and lead to recovery of function. Late in 2014 Parmar reported the creation of even better A9 neurons. More stringently tested, they function as well as fetal cells, growing axons over equally long distances, targeting the correct areas and restoring motor function in rats. "Our hope is that they are ready for clinical trials in about three years," Parmar says.

Studer, too, is optimistic. He recently received a $15-million grant to perfect his technique and generate cell lines based on GMP (good manufacturing practice) guidelines. "Now we have a protocol that led us to say we might actually be ready," Studer says. In parallel with the work manufacturing large batches of cells, he plans to begin lining up patients for a clinical trial, most likely the first to use embryonic stem cells.

Scientists at International Stem Cell in Carlsbad, Calif., have taken a different approach. Late in 2014 they reported success creating safe and effective dopamine neurons from unfertilized eggs that are chemically induced to develop as if they had been fertilized, a process called parthenogenesis that avoids the use of embryos. The company is seeking regulatory approval to begin a clinical trial with its human parthenogenetic neural stem cells early in 2015.

One reason for sticking with embryonic stem cells is regulatory. "This is all new ground," says University of Cambridge's Barker. "Cells are not a drug, and they are not a device. What are they?" To date, stem cells have been regulated by line—a set of renewable cells that are cultured in one lab and deemed safe. If stem cells are produced for individual patients—using the full potential of the newest technology—and still are required to follow the same approval process as existing stem cell lines, the therapy would be cost-prohibitive. One solution is to approve a generic induced stem cell process rather than separate lines. Another answer, which sacrifices some immune response benefits, would be to create a bank of up to as many as 500 regulated stem cell lines derived from adult tissue, which could, Isacson says, be genetically matched to 75 to 90 percent of the population.

REVOLUTIONARY TREATMENT

IN THEIR UPCOMING TRIAL, Barker and his team of collaborators will implant fetal dopamine neurons into the brains of 20 patients in Europe and follow 130 other patients whose Parkinson's is progressing naturally. Learning from past procedural mistakes, the scientists have tightened the selection of patients, improved tissue preparation and placement, and rethought the length and follow-up for the multicenter trial. The TransEuro study is intended to provide proof of the principle that cell therapy can consistently repair the brain, Barker says. "The importance is the process, which we see as the stepping-stone to the next generation of cell-based therapies."

Despite its theoretical superiority, populating the brain with new dopamine cells is not yet obviously better than existing treatments such as DBS, which brings faster results. In addition, other treatments in development may prove feasible. For example, in early 2014 researchers at Imperial College London reported promising results from the first gene therapy trials for Parkinson's patients. In this treatment, doctors insert genes for dopamine-producing enzymes into the striatum, a part of the midbrain that contributes to movement control.

Many researchers believe, however, that the remaining hurdles in producing and validating stem cell therapy can be cleared for Parkinson's. To Rao, who in his post at the NIH oversaw all the work under way in regenerative medicine, the progress so far has been encouraging. "These are the first steps in what could be a revolutionary treatment," he says. SA

Lydia Denworth is a Brooklyn, N.Y.–based science writer and author of *I Can Hear You Whisper: An Intimate Journey through the Science of Sound and Language* (Dutton, 2014).

MORE TO EXPLORE

Fetal Dopaminergic Transplantation Trials and the Future of Neural Grafting in Parkinson's Disease. R. A. Barker et al. in *Lancet Neurology,* Vol. 12, No. 1, pages 84–91; January 2013.

Induced Pluripotent Stem Cell–Derived Neural Cells Survive and Mature in the Nonhuman Primate Brain. M. E. Emborg et al. in *Cell Reports,* Vol. 3, No. 3, pages 646–650; March 28, 2013.

Therapeutic Application of Stem Cell Technology toward the Treatment of Parkinson's Disease. K. Nishimura and J. Takahashi in *Biological and Pharmaceutical Bulletin,* Vol. 36, No. 2, pages 171–175; 2013.

Human ESC-Derived Dopamine Neurons Show Similar Preclinical Efficacy and Potency to Fetal Neurons when Grafted in a Rat Model of Parkinson's Disease. Shane Grealish et al. in *Cell Stem Cell,* Vol. 15, No. 5, pages 653–665; November 6, 2014.

California Institute for Regenerative Medicine: **www.cirm.ca.gov**

© 2015 Scientific American

ONCOLOGY

NEVER TOO OLD FOR CHEMO

As the number of elderly patients with cancer soars, researchers explore how best to treat them

By Claudia Wallis

FOR MY HALE AND HEARTY FATHER-IN-LAW, THE FIRST SIGN THAT something was wrong occurred at 88 years of age, when his ever reliable tennis serve kept landing astray. A series of medical tests soon revealed the worst: advanced, metastatic pancreatic cancer. Treatment might buy him a little time, his doctors told him, but that prospect did not outweigh his dread of spending his final days in a toxic and debilitating haze of chemotherapy. He quickly opted for hospice care and died with dignity less than two months later, surrounded by loved ones.

My own father learned he had bladder cancer at 91 and made a very different choice. He underwent the full trifecta of treatment: surgery to pare down a tumor that had already penetrated the bladder wall, plus seven weeks of chemotherapy and 35 radiation treatments to destroy lingering cancer cells. There were times when he regretted it, complaining of weakness and torpor, but 20 months after completing the clinical gauntlet, he is alive and going relatively strong, considering he is 93. His sister made a similar decision when faced with lymphoma at 88; she, too, is a survivor—at 91.

Twenty years ago few oncologists would have attempted aggressive therapies with 90-year-olds. No one used the term "granny death panel," but people in their ninth and 10th decades of life were seen as too fragile for treatment. Their cancers were often believed to be so slow-growing that something else might kill them first; it made little sense to put them through the ordeal and cost of treatment.

Those ideas have since largely fallen by the wayside. Now, as my own family experience suggests, the elderly—especially the very old—are the fastest-growing group of cancer patients in the U.S., thanks mostly to the aging of the general population, better screening, improved therapies and other changes in medical practice. More than half of U.S. cancer patients are older than 65, and by 2030 that figure will rise to 70 percent, according to a 2012 analysis. Understanding differences in how cancer develops and behaves in the elderly and determining which older patients can benefit from treatment—and which ones lack the resilience to tolerate it—are therefore increasingly urgent issues. Fortunately, research is beginning to answer these questions and provide badly needed tools for doctors, patients and families facing complex decisions about treatment.

A DISEASE OF AGING

LIVE LONG ENOUGH, and chances are about 40 percent that you will develop a potentially life-threatening malignancy. Although cancer certainly can and does strike young people, it is, by and large, a disease of aging—and the leading cause of death in Americans between 60 and 79 years old.

Risks for most types of cancer increase as we grow older for at least three reasons. First, we experience more cumulative exposure to the things that mess with DNA in ways that can lead to malignant growth: sunlight, radiation, environmental toxins and noxious by-products of metabolism. Second, older cells are more vulnerable to this damage—or less able to repair themselves. "Most aging cells develop genomic changes that make them more susceptible to the carcinogens in the environment," says oncologist Lodovico Balducci, who studies and treats cancer in the elderly at the Moffitt Cancer Center in Tampa, Fla.

Illustration by Richie Pope

© 2015 Scientific American

Third, the various housekeeping systems—such as the immune defenses—that keep our tissues healthy begin to break down with age, the equivalent of watchdogs falling asleep.

The old idea that cancer is less aggressive in the elderly is not entirely without merit: breast and prostate cancers tend to grow more slowly in older patients. But other types—colon and bladder cancer and certain leukemias, for example—are usually more aggressive and harder to treat. This may in part be because of certain age-related genetic mutations.

An older body also provides a different internal environment for the growth of cancer cells than a younger body does. Whereas the drop in estrogen and other sex hormones that occurs with age can slow the development of some breast and prostate tumors, at least one other common endocrine change—rising levels of insulin—does the opposite, stimulating tumor growth. In addition, older tissues tend to exhibit more chronic inflammation—a low-level infiltration of immune cells and substances. "This hallmark of many old tissues," explains Judith Campisi of the Buck Institute for Research on Aging in Novato, Calif., "will generally promote the growth of cancer."

No wonder, then, that people who are 75 and older have the highest cancer rates of all age groups. According to 2010 figures from the U.S. Centers for Disease Control and Prevention, tumors with the potential to invade other tissues are nearly three times as common in people 75 and older as in individuals between ages 50 and 64—and that does not include common skin cancers (basal and squamous cell types) that tend not to spread deep within the body and that also become more pervasive with advancing age.

GETTING TREATMENT RIGHT

DESPITE THE PREVALENCE of cancer in the elderly, treatment studies rarely include people older than 70, leaving doctors without clear guidance on what works best for such patients. "In geriatrics, we are always having to extrapolate from treatment guidelines based on younger people, but the gap is most extreme in cancer care," says Holly Holmes, a geriatrician—or specialist in aging—at the University of Texas M.D. Anderson Cancer Center. That gap may finally begin to close in the years ahead. In September 2013 a report on the "crisis in cancer care" from the Institute of Medicine recommended offering drug companies a patent extension of six months on new drugs that have been tested in the elderly; a similar incentive has greatly increased the testing of drugs in children. Without such changes, Holmes notes, "we'll continue to test therapies only in the fittest people and get information that cannot be applied to older patients."

In the meantime, though, some researchers have designed tools that can help physicians and patients make informed decisions. Doctors such as Holmes and Balducci, who treat a lot of elderly patients, generally agree that chronological age alone is a poor indicator of how someone will respond to cancer treatment. What is more revealing, they say, is the patient's physiological age—a broad measure of health and well-being—and something called physiological reserve, which is essentially the ability to withstand stress, including the stress of surgery and chemotherapy. Doctors can best determine these attributes with a tool called a comprehensive geriatric assessment, a multifaceted inventory of the patient's strengths and weaknesses that looks at how well the body is operating. The assessment takes into account chronic diseases, medications, cognitive ability, nutritional status and social support. It also examines the patient's ability to function in the world: whether or not he or she needs help with what doctors call "activities of daily living" (getting out of bed, dressing, bathing, eating, toileting) and with such "instrumental activities" as managing money and medications, cooking, doing laundry and negotiating public transportation.

Much like the developmental milestones that pediatricians use to assess a toddler's health, activities of daily living involve multiple body systems working together and are therefore remarkably revealing of an older person's health—and predictive of the ability to tolerate treatment, says geriatric oncologist Arti Hurria of the City of Hope Comprehensive Cancer Center in Duarte, Calif. Unfortunately, such thorough assessment is rarely available outside of major medical centers. To address that problem, Hurria and her colleagues have developed a self-administered version that takes patients a median of just 22 minutes to complete. They have also devised and tested a tool for determining chemotherapy tolerance in older patients, published in 2011 in the *Journal of Clinical Oncology*. "It's 11 questions, and it's not hard to do," says Hurria, who just completed a two-year term as president of the International Society of Geriatric Oncology. She sees it as a tool to help oncologists refine their treatment plans for elderly patients. Balducci and his colleagues at Moffitt have developed a similar tool.

The idea is to give more guidance to doctors who are otherwise forced to improvise. In elderly cancer patients like my father and aunt, who suffer from a variety of chronic health problems, physicians often modify standard treatment regimens—perhaps using two chemotherapy drugs instead of three or lowering standard dosages—in the hope that the revised treatment will work well enough. The 11-question tool leads to a score that predicts—on a scale from 0 to 100 percent—the risk of severe side effects from chemotherapy. "If the risk score is very high, you might decide, after discussion with the patient, on a less aggressive approach," says oncologist William Tew of Memorial Sloan Kettering Cancer Center in New York City. Having a clearer idea of the patient's risk profile, he says, is especially critical when dealing with cancer that has spread from its original site in the body because such cases tend to require prolonged and arduous therapy.

Tools for predicting response also provide a framework for conversations with the patient and his or her loved ones about how much risk—and what kind of risk—they feel is appropriate. A young patient may be willing to tolerate extreme side effects and long hospitalizations for a chance to live longer. For an elderly patient, having to enter a nursing home because of side effects might seem like a fate worse than dying. Hurria and Holmes say they spend about equal amounts of time persuading octogenarian patients to consider treatment and warning them about taking on too much risk. "Sometimes we say, 'You're actually really fit,'" Holmes says. "'Maybe you'd like to treat the cancer as if you were a 55-year-old.'" As elderly survivors like my father can attest, having lived many years in no way disqualifies you from gunning for more time. SA

Claudia Wallis is an award-winning science journalist whose work has appeared in *Time*, *Fortune*, the *New York Times*, and other national publications.

© 2015 Scientific American

© 2015 Scientific American

BIOLOGY

A NEW PATH TO LONGEVITY

Researchers have uncovered an ancient mechanism that retards aging. Drugs that tweaked it could well postpone cancer, diabetes and other diseases of old age

By David Stipp

Photograph by Evan Kafka

© 2015 Scientific American

ON A CLEAR NOVEMBER MORNING IN 1964 THE ROYAL CANADIAN NAVY'S *CAPE SCOTT* embarked from Halifax, Nova Scotia, on a four-month expedition. Led by the late Stanley Skoryna, an enterprising McGill University professor, a team of 38 scientists onboard headed for Easter Island, a volcanic speck that juts out from the Pacific 2,200 miles west of Chile. Plans were afoot to build an airport on the remote island, famous for its mysterious sculptures of enormous heads, and the group wanted to study the people, flora and fauna while they remained largely untouched by modernity.

The islanders warmly welcomed Skoryna's team, which brought back hundreds of specimens of plants and animals, as well as blood and saliva from all 949 of the residents. But a test tube of dirt turned out to be the biggest prize: it contained a bacterium that made a defensive chemical with an amazing property—the ability to prolong life in diverse species.

Several research teams have now demonstrated that the chemical, named rapamycin, boosts the maximum life span of laboratory mice beyond that of untreated animals. Dubious antiaging claims are sometimes made based on data showing increased average life span, which can be achieved by antibiotics or other drugs that reduce premature death yet have nothing to do with aging. In contrast, increased *maximum* life span (often measured as the mean life span of the longest-lived 10 percent of a population) is a hallmark of slowed aging. No other drug has convincingly extended maximum life span in any of our mammalian kin—gerontology's long-awaited version of breaking the sound barrier. The success in mice has therefore been a game changer for scientists who study aging and how to mitigate its effects. Gerontologists dearly want to find a simple intervention for slowing aging, not merely to increase longevity, but because putting a brake on aging would be a broad-brush way to delay or slow progression of so much of what goes wrong with us as we get old, from cataracts to cancer.

For years gerontologists' hopes of discovering antiaging compounds had been on a roller coaster. Optimism rose with the discovery of gene mutations that extend maximum life span in animals and with new insights into how calorie restriction produces the same effect in many species. Yet the advances, for all their promise, did not reveal any drugs that could stretch the outer limits of longevity in a mammal. Although calorie restriction, which involves nutritionally adequate near-starvation diets, can both do that and delay cancer, neurodegeneration, diabetes and other age-related disorders in mice, very stringent dieting is not a feasible option for slowing aging in most mortals.

In 2006 resveratrol, the famous ingredient in red wine that replicates some of calorie restriction's effects in mice, seemed likely to break through the barrier when it was shown to block the life-shortening consequences of high-fat diets in the rodents. But this substance, which is thought to act on enzymes known as sirtuins, later failed to extend maximum life span in mice fed normal diets. The disappointing picture suddenly brightened again when the rapamycin results were announced in mid-2009. A trio of labs jointly reported that rapamycin, by then known to inhibit cell growth, extended maximum life span by some 12 percent in mice in three parallel experiments sponsored by the National Institute on Aging. What is more, to gerontologists' amazement, the drug extended average survival by a third in old mice that were presumed to be too damaged by aging to respond.

Rapamycin's shattering of the life span barrier in mammals has riveted attention on a billion-year-old mechanism that appears to regulate aging in mice and other animals and may well do the same in humans. Its mainspring is a protein called TOR (*t*arget *o*f *r*apamycin) and the gene that serves as the protein's blueprint. TOR is now a subject of intense scrutiny in both gerontology and applied medicine because a growing number of

IN BRIEF

In 2009 scientists discovered that a drug called rapamycin could significantly extend life span in mice, doing so by interfering with the activity of a protein called mammalian TOR, or mTOR.
The finding is the most compelling evidence to date that mammalian aging can be slowed pharmaceutically, and it galvanized interest in mTOR's role in the aging process.
The result also highlighted a mystery: Why would suppressing cellular growth and replication—one effect of interfering with mTOR—extend life span?
Research into that question could lead to medicines that postpone or mitigate aging-related disorders—from Alzheimer's disease to cancer to heart failure—and perhaps even extend how long humans can live.

PRECEDING PAGES: HAIR AND MAKEUP BY NIKKI WANG

© 2015 Scientific American

animal and human studies suggest that suppressing the activity of the mammalian version (mTOR) in cells can lower the risk of major age-related diseases, including cancer, Alzheimer's, Parkinson's, heart muscle degeneration, type 2 diabetes, osteoporosis and macular degeneration. The remarkable diversity of potential benefits implies that if medicines able to target mTOR safely and reliably could be found, they might be used to slow the aging process in people, as rapamycin apparently has in mice and other species—a possibility with profound implications for preventive medicine. (Rapamycin itself, unfortunately, has side effects that probably preclude testing whether it slows human aging.)

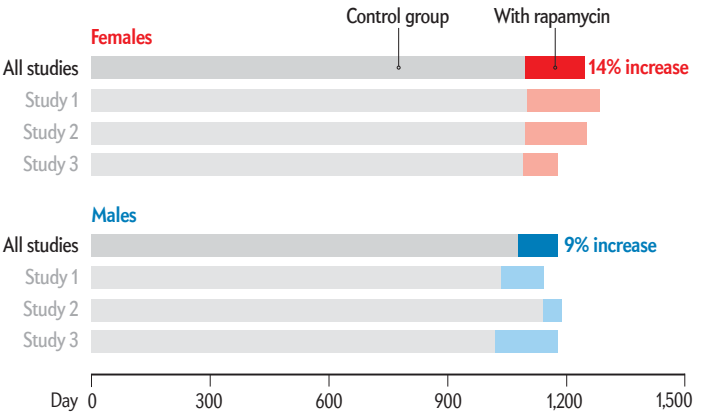
Similar predictions have been made for drugs that act on other molecules, notably the sirtuins. So what is different with mTOR? The finding that a drug has convincingly extended maximum life span in a mammal by acting on the molecule means that mTOR is central to mammalian aging and that researchers are now a lot closer than ever before to finding ways to brake the aging process. "It sure looks like [TOR] is the biggest game in town today and probably for the next decade," says Kevin Flurkey, a gerontologist at the Jackson Laboratory in Bar Harbor, Me., and a coauthor of the rapamycin study in mice.

TURNING POINT

The Making of Supermice

In 2009 three parallel experiments in mice showed that a drug called rapamycin extended the animals' maximum life span by 9 to 14 percent. ("Maximum life span" was defined as the average longevity of the oldest 10 percent of a population.) It was the first time a drug had convincingly boosted maximum longevity in a mammal. The feat has raised new hope that, one day, a simple medicine might retard aging and protect late-life health in humans, although rapamycin's side effects probably bar it from serving as that drug.

Longer Life for Mice



SOURCE: "RAPAMYCIN FED LATE IN LIFE EXTENDS LIFESPAN IN GENETICALLY HETEROGENEOUS MICE," BY DAVID E. HARRISON ET AL., IN *NATURE*, VOL. 460; JULY 16, 2009

TOR'S STORY

THE RESEARCH LEADING TO the discovery of TOR's influence on aging took shape when the Skoryna expedition turned over its soil samples to what was then Ayerst Laboratories in Montreal. Pharmaceutical researchers had been finding antibiotics in pinches of dirt since the 1940s, and so Ayerst's researchers screened the samples for antimicrobials.

In 1972 they sifted out a fungal inhibitor and named it rapamycin because Easter Island is also known locally as Rapa Nui. Ayerst initially hoped to use it to treat yeast infections. But then, scientists exploring its properties in cell-culture studies and on animals' immune systems found that it can hinder proliferation of immune cells, prompting its development instead to prevent immune rejection of transplanted organs. In 1999 rapamycin received U.S. Food and Drug Administration approval for patients who had received a kidney transplant. In the 1980s researchers also learned that the drug inhibits tumor growth, and since 2007 two derivatives of it—Pfizer's temsirolimus and Novartis's everolimus—have been approved to treat various kinds of cancer.

Biologists found rapamycin's ability to depress proliferation of both yeast and human cells highly intriguing—it suggested that the compound suppresses the actions of a growth-regulating gene conserved across the billion years of evolution between yeast and people. (Cells grow, expanding in size, when they are preparing to divide and proliferate.) In 1991 Michael N. Hall and his colleagues at the University of Basel in Switzerland identified the ancient target by discovering that rapamycin inhibits the effects of two growth-governing yeast genes, which they named *TOR1* and *TOR2*. Three years later a number of investigators, including Stuart Schreiber of Harvard University and David Sabatini, now at the Whitehead Institute for Biomedical Research in Cambridge, Mass., independently isolated the mammalian *TOR* gene. Many other species, including worms, insects and plants, are now known to possess *TOR* genes that govern cell growth.

Through the 1990s researchers learned much more about the gene's roles in cells and the body as a whole—many of which ultimately turned out to have a bearing on aging. They found, notably, that the gene encodes an enzyme, or catalytic protein, that combines in the cytoplasm with several other proteins to form a complex, called TORC1, which supervises a whole slew of growth-related activities in cells. Rapamycin mainly affects TORC1. A less well-understood, second complex, called TORC2, also incorporates the TOR enzyme.

The teams further demonstrated that TOR is a nutrient sensor. When food is abundant, its activity rises, prompting cells to increase their overall production of proteins and to divide. When food is scarce, TOR settles down, and the resulting reduction in overall protein manufacture and cell division conserves resources. At the same time, a process called autophagy amps up: cells break down defective components such as misshapen proteins and dysfunctional mitochondria (the cell's energy powerhouses), generating by-products that can be exploited as fuel or building materials; newborn mice rely on autophagy to supply energy before they start nursing. When food returns, the seesaw relation between TOR and autophagy swings back again: TOR activity rises, and autophagy slows.

Researchers also discovered that signaling pathways headed

Graphic by Jen Christiansen

© 2015 Scientific American

MECHANISM

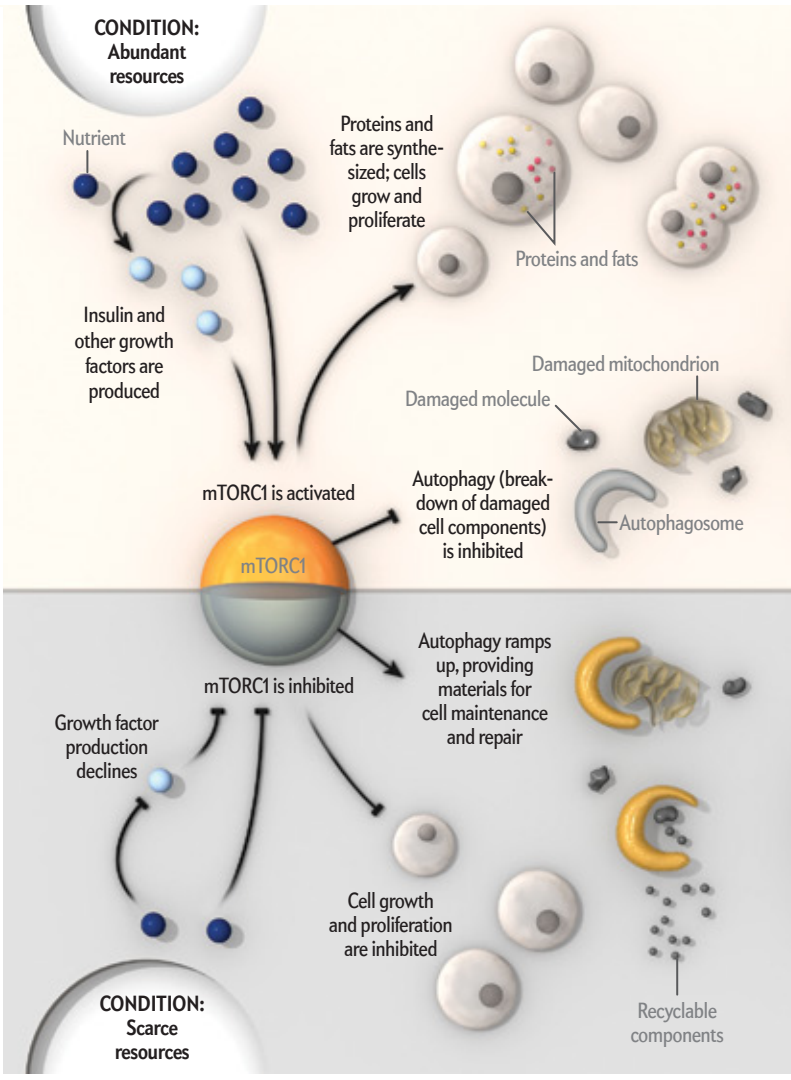
TOR Story: A Jekyll and Hyde Molecule

Rapamycin extends life in yeast and animals by inhibiting a protein called TOR; calorie restriction, too, slows aging in part by acting on TOR. Research into how the protein functions in cells and into why its inhibition slows aging indicates that TOR is both angelic and diabolical. It is a nutrient sensor critical to organismal growth and development early in life (*near right*). Yet its continued activity after maturity can impair cell function (*far right*) and thus damage tissues. Investigators suspect that these late-life effects on TOR contribute to aging and its associated diseases in humans. The figures here, which focus on mammalian TOR (mTOR), are highly simplified; mTOR is affected by and affects a complex network of molecules in cells. (The pointed arrows represent stimulation; the others represent inhibition.)

The Good Guy: A Key Nutrient Sensor Early in Life

Mammalian TOR exerts many of its effects as part of a complex called mTORC1. When food is plentiful (*top*), which evokes increased production of insulin and related proteins (known as growth factors), mTORC1 reacts to the nutrients and the growth factors by stimulating the synthesis of cellular components (especially proteins and fat) and prompting cell growth and division. At the same time, the complex instructs cells to pull back on autophagy—a process that degrades damaged mitochondria (the cell's energy factories) and molecules.

When food or other resources are scarce (*bottom*), mTORC1 quiets down, causing cells to focus on self-preservation over replication. Meanwhile autophagy increases to provide an emergency supply of raw materials for cellular repair and energy generation.


CONDITION: Abundant resources
Nutrient
Proteins and fats are synthesized; cells grow and proliferate
Proteins and fats
Insulin and other growth factors are produced
Damaged mitochondrion
Damaged molecule
mTORC1 is activated
Autophagy (breakdown of damaged cell components) is inhibited
Autophagosome
mTORC1
mTORC1 is inhibited
Autophagy ramps up, providing materials for cell maintenance and repair
Growth factor production declines
Cell growth and proliferation are inhibited
Recyclable components
CONDITION: Scarce resources

by TOR and insulin in animals are intertwined; signaling pathways are sequences of molecular interactions that control a cell's activities. Insulin is the hormone released by the pancreas after meals to signal muscle and other cells to absorb glucose from the blood for energy. But that is not all insulin does. It is a growth factor; both it and related proteins help to rev up the TOR pathway, a behavior that helps induce cells throughout the body to grow and proliferate in response to nutrient intake. In another feature important for health, the wiring between the TOR and insulin pathways includes a negative feedback loop: stimulating TOR makes cells less sensitive to insulin's signals. Chronic overeating, then, will activate TOR excessively and make cells increasingly deaf to insulin; this insulin "resistance," in turn, can lead to high blood glucose levels and diabetes and can also contribute to other age-related disorders, such as heart problems.

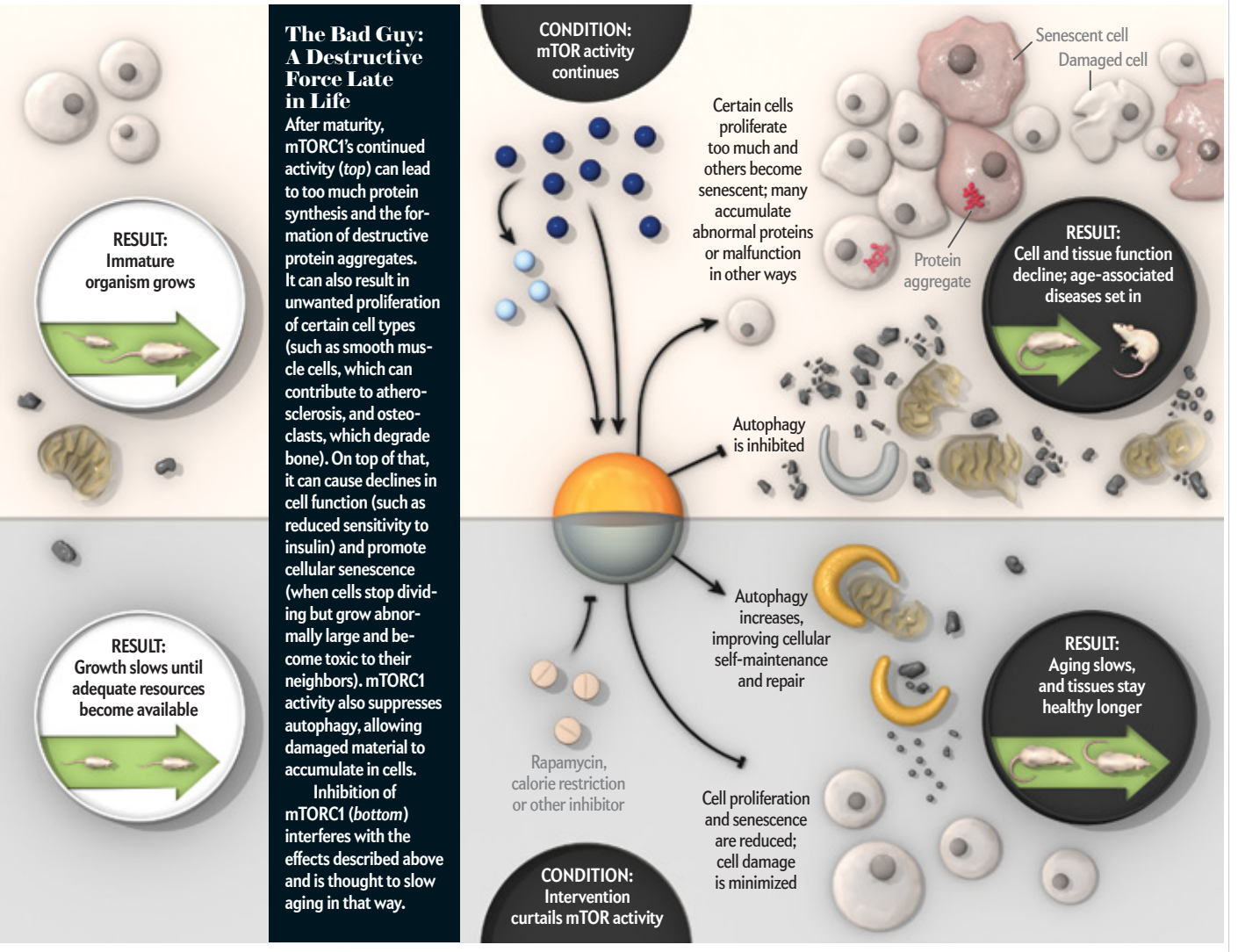
TOR also reacts to cellular stresses beyond nutrient shortages, including low oxygen levels and DNA damage. In general, when cells sense threats to survival, TOR activity dials back. The consequent slowing of protein production and cell proliferation frees up resources so that cells can channel them into DNA repair and other defensive measures. Studies in fruit flies indicate that as protein synthesis gets broadly curtailed in this red-alert mode, protein manufacturing also shifts in a way that leads to selective production of key mitochondrial components, perhaps helping cells rejuvenate their energy systems. No doubt this multifaceted "stress response" evolved to help cells cope with harsh conditions, but it may also inadvertently harden them against the ravages of time.

FINDING THE AGING LINK

THE IDEA THAT TOR influences aging dates from findings in the mid-1990s indicating that nutrient-starved cells curtail growth by reducing TOR activity. Gerontologists had seen something like this before: in 1935 Cornell University nutritionist Clive McCay showed that putting young rats on near-starvation diets made them slow-growing *and* extraordinarily long-lived. Calorie restriction has since been shown to extend maximum life span in species ranging from yeast to spiders to dogs; preliminary evidence suggests that it may also do so in monkeys, but the data thus far are not consistent. Cutting normal calorie in-

Illustration by Emily Cooper

© 2015 Scientific American


The Bad Guy: A Destructive Force Late in Life
After maturity, mTORC1's continued activity (*top*) can lead to too much protein synthesis and the formation of destructive protein aggregates. It can also result in unwanted proliferation of certain cell types (such as smooth muscle cells, which can contribute to atherosclerosis, and osteoclasts, which degrade bone). On top of that, it can cause declines in cell function (such as reduced sensitivity to insulin) and promote cellular senescence (when cells stop dividing but grow abnormally large and become toxic to their neighbors). mTORC1 activity also suppresses autophagy, allowing damaged material to accumulate in cells.
Inhibition of mTORC1 (*bottom*) interferes with the effects described above and is thought to slow aging in that way.
CONDITION: mTOR activity continues
Certain cells proliferate too much and others become senescent; many accumulate abnormal proteins or malfunction in other ways
Senescent cell
Damaged cell
Protein aggregate
RESULT: Cell and tissue function decline; age-associated diseases set in
RESULT: Immature organism grows
Autophagy is inhibited
Autophagy increases, improving cellular self-maintenance and repair
RESULT: Aging slows, and tissues stay healthy longer
RESULT: Growth slows until adequate resources become available
Rapamycin, calorie restriction or other inhibitor
Cell proliferation and senescence are reduced; cell damage is minimized
CONDITION: Intervention curtails mTOR activity

take by about a third early in life generally boosts maximum life span by 30 to 40 percent, apparently by postponing the deterioration of aging; elderly rhesus monkeys in long-term studies of calorie restriction are extraordinarily healthy and youthful-looking for their ages.

The approach does not always work—in some strains of lab mice, it actually shortens life—but mounting evidence implies that calorie restriction can promote healthy aging in people just as it does in monkeys. Thus, identifying compounds that evoke calorie restriction's effects without inducing hunger is a grail for scientists who study aging.

By the early 2000s researchers knew enough about TOR's functions to suspect that blocking its influence in cells might mimic calorie restriction. In 2003 Tibor Vellai, a Hungarian researcher visiting at the University of Fribourg in Switzerland, led a roundworm study offering the first evidence that inhibiting TOR may oppose aging: by genetically suppressing TOR synthesis in worms, he and his colleagues more than doubled the worms' average life span. A year later a study at the California Institute of Technology led by Pankaj Kapahi, now at the Buck Institute for Research on Aging in Novato, Calif., demonstrated that quelling TOR activity in fruit flies extended their average life span, too, and protected them from the consequences of rich diets, just as calorie restriction does. And in 2005 Brian Kennedy, then at the University of Washington, and his colleagues hammered home the link between TOR and aging by showing that disabling various TOR pathway genes in yeast cells increased longevity.

These studies, along with others on TOR, were especially intriguing because they suggested that inhibition of TOR mimics not only calorie restriction but also mutant genes known to extend life span. The first such "gerontogenes" had been discovered about a decade earlier in roundworms whose mean and maximum life spans were doubled by mutations later shown to interrupt their species' version of insulin signaling. The discovery that aging, previously thought to be intractably complex, could be dramatically slowed by altering a single gene had helped make gerontology a hot topic; among other things, it suggested that human aging might be retarded with drugs. That idea was reinforced by the discovery of various mouse

© 2015 Scientific American

gerontogenes in the late 1990s and early 2000s that block growth signals, including ones conveyed into cells by insulin and a closely related hormone called insulinlike growth factor 1. In 2003 a mouse with one such mutation set the record for its species' longevity: nearly five years. Lab mice generally live less than 30 months.

You might think the connections between TOR, calorie restriction and gerontogenes would have inspired a heated race to test rapamycin's life-extending effect in mammals. Yet experts on mammalian aging "didn't really take TOR seriously" before the late 2000s, says Steven Austad, a gerontologist at the University of Alabama at Birmingham. The reason is that rapamycin was known as an immunosuppressant; hence, long-term administration, it was widely assumed, would be toxic to mammals. Still, Zelton Dave Sharp, one of Austad's independent-minded colleagues at the Barshop Institute for Longevity and Aging Studies at the University of Texas Health Science Center at San Antonio, concluded otherwise after studying the TOR literature. In 2004 he instigated a major study on life span in mice that were chronically dosed with rapamycin.

Funded by the National Institute on Aging, the study seemed to go badly at first—trouble formulating the drug in mouse chow delayed the initiation of doses until the study's rodents were 20 months old, the human equivalent of 60 years. At that point, Austad says, "no one—and I mean no one—really expected it to work." Indeed, not even calorie restriction reliably extends life span in such old animals. But in 2009 three gerontology labs that jointly conducted the study—Randy Strong's at the Barshop Institute, David E. Harrison's at the Jackson Laboratory and Richard A. Miller's at the University of Michigan—made history by reporting that the drug had upped life expectancy by an astounding 28 percent in the aged male rodents and 38 percent in the females versus control animals. Maximum life span was increased by 14 percent in females and 9 percent in males.

The galvanizing mouse results were followed by others highlighting TOR's importance in aging. Rapamycin has now been shown to extend mouse life span in at least six labs around the world. Studies have also shown that it promotes healthy aging in the rodents, delaying the onset of degenerative changes in the liver and heart, slowing age-related cognitive decline, blocking cancer and preventing loss of immune function. The three U.S. labs that first tested rapamycin in mice also reported that initiating doses in the rodents at nine months of age extended their life spans by about the same amount that starting them at 20 months did—suggesting that rapamycin mainly confers benefits after midlife, possibly because that is when the deterioration it opposes mostly occurs.

The fact that inhibiting TOR prolongs life across species now stands out like a beacon in the molecular murk surrounding aging. That prominence does not mean, however, that other aging-related pathways are unimportant for longevity. Indeed, gerontologists increasingly picture the pathways that calorie restriction affect as belonging to a complex, many-pronged network that can be tweaked in various ways to promote healthy aging. The network's components include insulin-related enzymes and proteins called FoxOs that activate stress responses in cells. Considerable evidence also indicates that sirtuins help to induce calorie restriction's benefits in mammals and may, in some circumstances, participate in TOR inhibition. At this point, though, TOR appears to be the closest thing to the network's central processing unit, integrating various inputs to control the rate of aging, at least in various animal species and perhaps humans, too.

AN ENIGMA UNRAVELS

IN TRYING TO BETTER understand how TOR inhibition and calorie restriction extend life span in so many species, researchers have come up against a long-standing mystery: Why would any mechanism evolve to retard aging?

The issue has evolutionary biologists scratching their heads because natural selection works to foster successful reproduction, not to enable organisms to go into overtime in the game of life by remaining vibrant at ages when members of their species have typically been wiped out by predators, infections, accidents, and the like. Because of such "extrinsic" risks to survival, evolution effectively equips creatures to live long enough to reproduce before the environment does them in; then, as their odds of continued survival decline, they deteriorate like abandoned houses. Yet calorie restriction retards late-life decline in widely differing species, which implies that it evokes an ancient, conserved mechanism that has been shaped by natural selection to slow aging under some circumstances.

SOME GERONTOLOGISTS THINK ANOTHER SOLUTION TO THE CONUNDRUM MAKES MORE SENSE: CALORIE RESTRICTION EXTENDS LIFE SPAN AS A SIDE EFFECT OF RESPONSES EVOLVED FOR PURPOSES UNRELATED TO AGING.

A frequently cited solution to the puzzle holds that calorie restriction taps an evolved starvation response that brakes organisms' aging during lean times so they can last long enough to reproduce when conditions improve. Skeptics, such as Alabama's Austad, counter that there is no evidence that low-calorie diets make animals in the wild live longer; calorie restriction has been observed to extend life span only in pampered lab animals. Already lean wild animals weakened by hunger may have little chance of surviving long enough to benefit from, and pass on, genes that slow aging and thus give rise to an evolved starvation response.

Some gerontologists think another solution to the conundrum makes more sense: calorie restriction extends life span as a side effect of responses evolved for purposes unrelated to aging. Austad, for example, theorizes that during lean times, animals branch out and eat unfamiliar things in the wild, exposing themselves to toxic substances not present in their regular food. Such "hard foraging" might have selected for a tendency to rev up inner defenses against poisons as hunger sets in, activating the cellular stress-response and repair processes that accompany it and thereby inadvertently slowing aging.

A few years ago Mikhail V. Blagosklonny, a cancer researcher at the Roswell Park Cancer Institute in Buffalo, N.Y., seized on discoveries about TOR to propose another theory that explains

© 2015 Scientific American

calorie restriction's magic as a kind of accident. A native of Russia whose work has ranged widely across cancer research and cell biology, he was inspired by an unorthodox idea: the capacity for growth, which seems the very essence of youthfulness, drives us into the grave later in life. Calorie restriction prolongs life, he posits, by interfering with the untoward, late-life effects of growth pathways, TOR's most important among them.

Blagosklonny's theory holds that TOR, which is essential for development and reproduction, becomes the engine of aging after maturity is reached. Because of its progrowth signaling, it abets proliferation of smooth muscle cells in arteries (a key step in atherosclerosis), accumulation of fat (which helps to spur body-wide inflammation), development of insulin resistance, multiplication of cells called osteoclasts that break down bones, and growth of tumors. Further, by diminishing autophagy, TOR favors the buildup of aggregation-prone proteins and of dysfunctional mitochondria, which spew DNA-damaging free radicals and hurt cells' energy metabolism. It also contributes to the accumulation of degradation-resistant proteins in neurons, a process that plays a part in Alzheimer's and other forms of neurodegeneration. Blagosklonny has shown that, late in life, TOR's signals can also help trigger cell senescence, a kind of night-of-the-living-dead state that damages nearby cells and saps tissues' regenerative capacity.

All this shows, Blagosklonny argues, that evolution has not built a mechanism designed to slow aging. Rather the life-extending effects of rapamycin, calorie restriction and gene mutations that block progrowth hormones are merely accidents of nature—ones that happen to interfere with what he calls the "twisted growth" of aging, causing it to play out more slowly than usual. In effect, the TOR pathway behaves very much like an aging program even though it was built to aid early development.

Although Blagosklonny's theory is novel, one of its key inspirations was a well-regarded hypothesis proposed in 1957 by the late evolutionary biologist George Williams. He theorized that aging is caused by two-faced genes that are beneficial early in life but harmful later on. Such "antagonistic pleiotropic genes" are favored by evolution because, as Williams put it, natural selection is "biased in favor of youth over old age whenever a conflict of interest arises." Blagosklonny sees *TOR* as the quintessential example of such genes.

Like many novel theories, Blagosklonny's is controversial. It strikes certain scientists as putting too much weight on TOR, whereas others see aspects of TOR distinct from growth promotion as the key thing—for instance, some regard TOR's inhibition of autophagy, which renews cellular components, as its dominant influence on aging. Still, some TOR experts find the theory plausible, and Basel's Hall gives Blagosklonny credit for "connecting dots that others don't even see"—adding, "and I am inclined to think he is right."

TOR AND MEDICINE'S FUTURE

IF TOR IS A KEY DRIVER of aging, what are the options for defanging it? Rapamycin's side effects may rule it out as a candidate antiaging drug in people because, among other things, it can pose risk of infection, cause anemia and increase blood glucose.

Another drug, metformin, might be an alternative, although much testing would be needed to evaluate the idea. Metformin is the most widely prescribed diabetes drug—millions have safely taken it for long periods to lower blood glucose. Its mechanism of action is not well understood, but it is known to inhibit the TOR pathway. Research groups in the U.S. and Russia have independently found that metformin modestly increases longevity in mice. Further, a 2014 study involving data from more than 78,000 diabetes patients on the drug found that their median survival time was 15 percent greater than that of control subjects without diabetes. Indeed, because metformin's wide use among diabetics has inadvertently lowered their risk of tumors, the drug has prevented more cancer deaths than any other medicine, according to one estimate. But whether it can slow aging in people is not known.

Boosting human longevity proportional to rapamycin's enhancement of mouse life span could potentially add, on average, five to 10 years to a human life. That would be huge. Indeed, life expectancy in the developed world has risen so much over the past century that when it comes to aging, we are like Olympic athletes trying to eke out ever smaller incremental gains—average life span in the U.S. rose by more than 50 percent during the 20th century; over the past decade it rose by less than 2 percent.

Because we have cut early-life mortality about as low as it can go, boosting life expectancy much at this point will require pushing back diseases of aging. The exploding costs of geriatric medicine suggest this is a very tall order. But drugs that slowed aging could affordably manage it. In effect, they would serve as preventive medicines that could postpone or retard our late-life ills—dementia, osteoporosis, cataracts, cancer, loss of muscle mass and strength, deafness, even wrinkles—just as medicines that cut blood pressure and cholesterol now help to push off middle-age heart attacks. And they would buy us quality time, extending our period of vibrancy before we become frail and die.

Developing such drugs would not be easy. One obstacle is the lack of a reliable way to measure the rate of human aging; a good yardstick would enable researchers to test efficacy without having to run untenably long trials. Yet finding safe antiaging medicines would be worth the effort, if only to promote healthy aging irrespective of increasing longevity. Who would have thought that a vial of dirt scooped up five decades ago would become such fertile soil for research that could lead to more years of quality life? SA

David Stipp is a Boston science writer focused on gerontology. An updated, paperback version of his book on the subject, *The Youth Pill: Scientists at the Brink of an Anti-Aging Revolution,* was published in 2013.

MORE TO EXPLORE

Growth and Aging: A Common Molecular Mechanism. Mikhail V. Blagosklonny and Michael N. Hall in *Aging,* Vol. 1, No. 4, pages 357–362; April 20, 2009. www.ncbi.nlm.nih.gov/pubmed/20157523

Rapamycin Fed Late in Life Extends Lifespan in Genetically Heterogeneous Mice. David E. Harrison et al. in *Nature,* Vol. 460, pages 392–395; July 16, 2009.

Aging and TOR: Interwoven in the Fabric of Life. Zelton Dave Sharp in *Cellular and Molecular Life Sciences,* Vol. 68, No. 4, pages 587–597; February 2011. www.ncbi.nlm.nih.gov/pubmed/20960025

Rapalogs and mTOR Inhibitors as Anti-aging Therapeutics. Dudley W. Lamming et al. in *Journal of Clinical Investigation,* Vol. 123, No. 3, pages 980–989; March 1, 2013. www.ncbi.nlm.nih.gov/pmc/articles/PMC3582126

© 2015 Scientific American

© 2015 Scientific American

NEUROSCIENCE

SEEDS OF DEMENTIA

A chain reaction of toxic proteins may help explain Alzheimer's, Parkinson's and other killers—an insight that could lead to desperately needed new treatment options

By Lary C. Walker and Mathias Jucker

UNDER A MICROSCOPE, A PATHOLOGIST SEARCHING THROUGH THE DAMAGED NERVE cells in a brain tissue sample from a patient who has died of Alzheimer's disease can make out strange clumps of material. They consist of proteins that clearly do not belong there. Where did they come from, and why are there so many of them? And most important, what do they have to do with this devastating and incurable disorder? The search for answers has turned up a startling discovery: the clumped proteins in Alzheimer's and other major neurodegenerative diseases behave very much like prions, the toxic proteins that destroy the brain in mad cow disease.

IN BRIEF

A Nobel Prize–winning discovery found that mad cow and related infectious diseases occur when aberrant proteins—prions—wreak havoc by causing normal versions of those proteins to become malformed.

Prionlike disease processes also appear to be at work in major neurodegenerative disorders, including Alzheimer's, Parkinson's and Lou Gehrig's, although they are not transmitted from person to person.

How proteins contort into a form that causes others to undergo a similar transformation may lead to new approaches to preventing and treating some of the world's leading neurological illnesses.

Illustration by Ronald Kurniawan

© 2015 Scientific American

Prions are misshapen yet durable versions of proteins normally present in nerve cells that cause like proteins to misfold and clump together, starting a chain reaction that eventually consumes entire brain regions. In the past 15 years scientists have learned that such a process may be at work not only in mad cow and other exotic diseases but also in major neurodegenerative disorders, including Alzheimer's, Parkinson's, amyotrophic lateral sclerosis (also known as ALS or Lou Gehrig's disease), and the concussion-related dementia of football players and boxers.

Alzheimer's and Parkinson's, all evidence suggests, are not contagious like mad cow or, for that matter, the flu. Rather the significance of these recent findings is that they provide scientists with a prime suspect for a slew of devastating brain disorders—a signpost that points toward a pathway for eventual treatments. Drugs developed for Alzheimer's might be used directly—or else inspire new pharmacology—for Parkinson's, traumatic brain injury or other terrifying conditions that rob an individual of a basic sense of self—good news for tens of millions worldwide who suffer from neurodegenerative disorders.

The new thinking owes a debt to research that first led to the discovery of prions. It began in the early 18th century, with reports of a curious, fatal disease of sheep called scrapie, so named because affected animals compulsively rubbed the wool from their skin. Later, as scientists began to investigate the disease, they noticed under the microscope that the nervous system was shot through with holes. In the 1930s French and British researchers determined that scrapie could be transmitted from one sheep to another, but the infectious agent was elusive and behaved strangely: the incubation time between exposure and symptoms was much longer than for conventional disease-causing agents such as bacteria or viruses, and the immune response that usually kicks in to eliminate such invaders seemed to be absent.

Those oddities were a hint that the usual suspects were not the cause, but for about 20 years after these reports scrapie remained just an obscure veterinary malady. In the 1950s, though, William Hadlow, then at the British Agricultural Research Council Field Station at Compton, noted conspicuous similarities in brain pathology between scrapie and a mystifying human disease called kuru. Kuru is a progressive neurodegenerative disease, mainly confined to the Fore people of Papua New Guinea, in which a steady decline in coordination and mental function invariably ends in death. The disease among the Fore was ultimately found to result from the ritual cannibalism of tribe members who had died of the disease, which implied that some infectious agent was at fault and somehow reached the brain from elsewhere in the body.

In the 1960s D. Carleton Gajdusek of the U.S. National Institutes of Health and his colleagues confirmed that the disease was transmissible, showing that kuru could be conveyed by the direct injection of brain material from victims of the disease into the brains of nonhuman primates. Gajdusek's team also recognized key parallels in brain pathology between kuru and another neurodegenerative brain disorder: Creutzfeldt-Jakob disease (CJD), a rapidly progressive type of dementia that occurs in roughly one in a million people worldwide. Gajdusek went on to demonstrate that CJD is transmissible to primates in the same way as kuru, although CJD most often arises in people spontaneously.

In the 1980s Stanley B. Prusiner of the University of California, San Francisco, identified the agent responsible for scrapie and related disorders, which are known collectively as spongiform encephalopathies for the way they cause the brain to take on the appearance of Swiss cheese. In a beautiful series of experiments, he and his co-workers amassed persuasive evidence that the infectious agent consists solely of a misfolded version of an otherwise innocuous protein called PrP. Prusiner also coined the term "prion" (pronounced "pree-on") at that time, for "proteinaceous infectious particle," to distinguish protein agents that spread disease on their own from viruses, bacteria, fungi and other known pathogens. (Today the term is expanding to include other proteins that impose their shape on like proteins and does not necessarily imply infectiousness.) Prusiner's ideas sparked a huge controversy when he proposed that a protein could transmit disease, but in 1997 his efforts were rewarded when he won the Nobel Prize for this work.

Recently in-depth research into Alzheimer's and other neurodegenerative conditions indicates that these disorders, though lacking the infectiousness of classic prion diseases, may arise and amplify in the brain in a similar way; that is, by a process we call pathogenic protein seeding. Like the prions responsible for scrapie and its kin, the proteinaceous seeds can be released, taken up and transported by cells, which may explain how disease spreads from one place to another. These commonalities suggest that the prion paradigm could soon unify our thinking about how seemingly diverse diseases arise and wreak havoc.

IS MISFOLDING BEHIND ALZHEIMER'S?

THE FIRST HINT of this connection came as far back as the 1960s, when researchers struggling to grasp the mysteries of prion diseases began to notice some suggestive similarities to the brain changes that occur in other neurodegenerative disorders, especially Alzheimer's. The most common cause of dementia in aging humans, Alzheimer's appears stealthily and progresses relentlessly over the course of many years, robbing the victim of memory, personality and, ultimately, life itself. The incidence of Alzheimer's doubles every five years after the age of 65 until, by 85 years, nearly one in three adults is afflicted.

Researchers of the time also understood that protein clumping was involved. In 1906 Alois Alzheimer, after whom the disease is named, associated dementia with two peculiar microscopic abnormalities in the brain: senile plaques (now known to be clumps of a misfolded protein fragment named amyloid-beta, or Aβ), located outside of cells, and neurofibrillary tangles (filaments composed of aggregations of a protein called tau), located inside the cell. When these clumps are highly magnified with an electron microscope, the proteins can be seen to form long fibers made up of Aβ or tau. In addition, the proteins form smaller assemblies known as oligomers and protofibrils that can also interfere with the normal function of neurons.

In the late 1960s Gajdusek's team set out to test the hypothesis that Alzheimer's, like scrapie, kuru and Creutzfeldt-Jakob, might be transmissible—so they injected processed brain matter from Alzheimer's patients into the brains of nonhuman primates. Independently, a team led by Rosalind Ridley and Harry Baker, then at the Clinical Research Center in Harrow, England, later undertook similar experiments. The results of the Gajdusek studies were indeterminate, and neither group reported that it had triggered fully developed Alzheimer's. The British researchers, however, found a hint of an effect: after an incuba-

© 2015 Scientific American

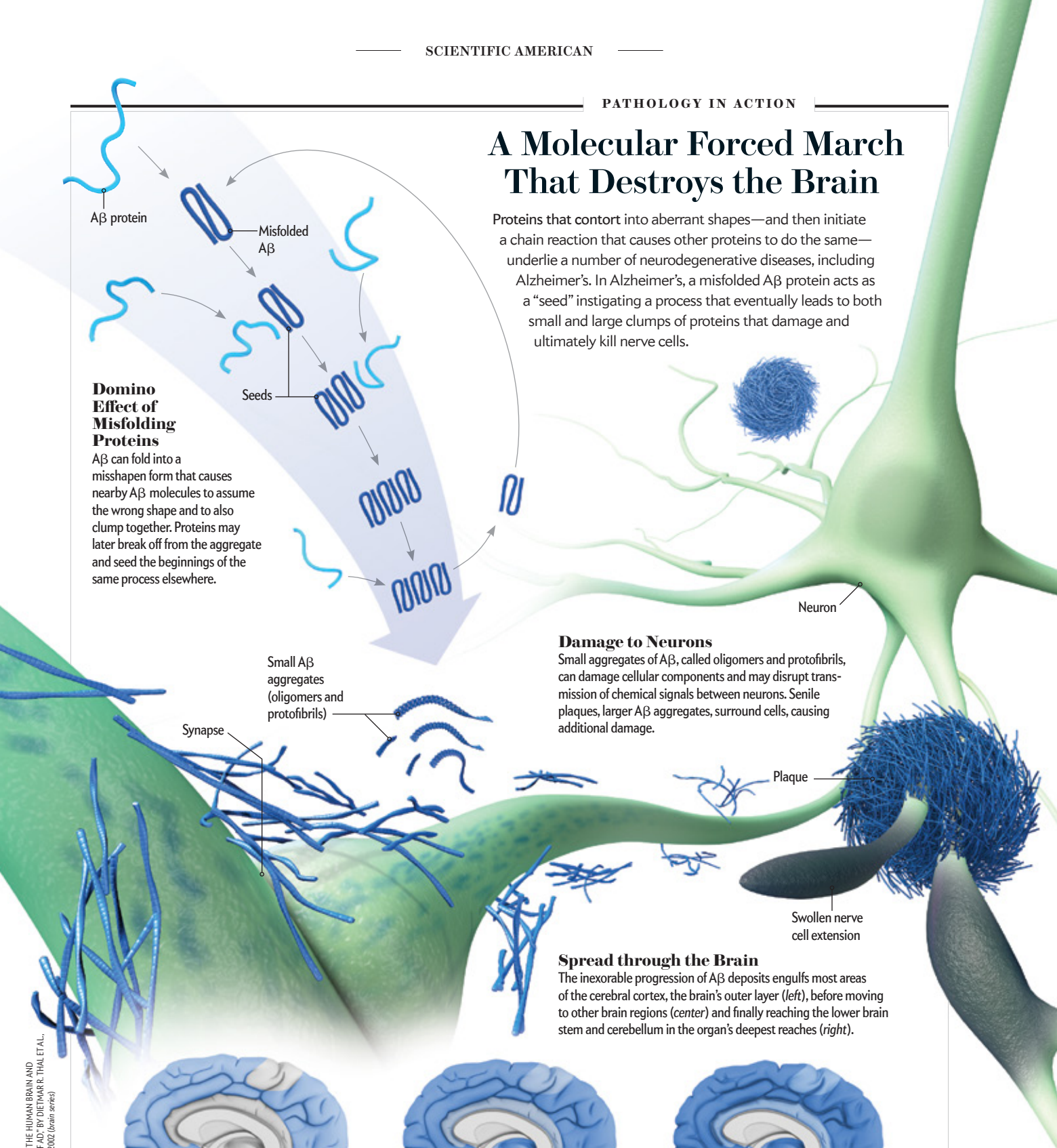
PATHOLOGY IN ACTION

A Molecular Forced March That Destroys the Brain

Proteins that contort into aberrant shapes—and then initiate a chain reaction that causes other proteins to do the same—underlie a number of neurodegenerative diseases, including Alzheimer's. In Alzheimer's, a misfolded Aβ protein acts as a "seed" instigating a process that eventually leads to both small and large clumps of proteins that damage and ultimately kill nerve cells.

Domino Effect of Misfolding Proteins

Aβ can fold into a misshapen form that causes nearby Aβ molecules to assume the wrong shape and to also clump together. Proteins may later break off from the aggregate and seed the beginnings of the same process elsewhere.



Damage to Neurons

Small aggregates of Aβ, called oligomers and protofibrils, can damage cellular components and may disrupt transmission of chemical signals between neurons. Senile plaques, larger Aβ aggregates, surround cells, causing additional damage.

Spread through the Brain

The inexorable progression of Aβ deposits engulfs most areas of the cerebral cortex, the brain's outer layer (*left*), before moving to other brain regions (*center*) and finally reaching the lower brain stem and cerebellum in the organ's deepest reaches (*right*).

SOURCE: "PHASES OF Aβ-DEPOSITION IN THE HUMAN BRAIN AND ITS RELEVANCE FOR THE DEVELOPMENT OF AD," BY DIETMAR R. THAL ET AL. IN *NEUROLOGY*, VOL. 58, NO. 12; JUNE 25, 2002 (*brain series*)

Illustration by AXS Biomedical Animation Studio

© 2015 Scientific American

tion period of at least five years, Aβ plaques were more abundant in marmosets that had received the processed Alzheimer's brain matter than in a comparison group of control marmosets.

At this point, our research groups considered initiating studies to see if misfolded Aβ—in the form of small aggregates—acted as a seed that set off a chain reaction of protein misfolding and clumping that eventually led to the type of protein deposits that overwhelm the brain in Alzheimer's. But we were discouraged by the five years or so it took to incubate seeded plaque formation in monkeys.

Our outlook changed considerably in the mid-1990s with the advent of "transgenic" mice that were genetically engineered to produce the precursor protein from which the human Aβ fragment is generated—APP (for amyloid precursor protein). Together with a talented group of colleagues and students, we began a series of experiments exploring the Aβ-seed hypothesis in these mice. The transgenic animals do not embody all features of Alzheimer's (which appears to be unique to humans), but they offer considerable advantages for our experiments: they are small, easy to maintain and short-lived, and each transgenic mouse spontaneously develops Aβ brain deposits at a relatively consistent age.

OUR RESEARCH TEAM SET OUT TO SEE IF MISFOLDED PROTEINS ACT AS SEEDS THAT SET OFF A CHAIN REACTION THAT EVENTUALLY PRODUCES TOXIC DEPOSITS THAT OVERWHELM THE BRAIN.

In our studies, we concentrated on Aβ rather than tau because even though plaques and tangles both contribute to the neurodegeneration that causes dementia in Alzheimer's, much of the evidence implies that misfolded Aβ is a key catalyst for the disease's development. Indeed, many of the risk factors for Alzheimer's influence cellular processes involved with the production, folding, aggregation or removal of Aβ. Genetic mutations that cause disease onset at a very early age alter APP or the enzymes that splice Aβ from that precursor. Scientists also now know that the brain begins to show signs of Alzheimer's a decade or more before the symptoms appear—and that the abnormal clumping of proteins occurs very early in the disease process [see "Alzheimer's: Forestalling the Darkness," by Gary Stix, on page 66]. Aware that the accumulation of misfolded Aβ is pivotal to the development of Alzheimer's, we wanted to know what first spurs protein aggregation in the brain.

During our first experiments, we set out to determine whether extracts of brain tissue from patients who had died of Alzheimer's would initiate Aβ aggregation in the brains of APP-transgenic mice. In other words, could we induce and propagate Aβ aggregation in the same way that prions trigger PrP aggregation in the spongiform encephalopathies? Using methods developed for the study of those prions, we first took small brain samples from Alzheimer's patients or from control patients who had died of causes other than Alzheimer's. We ground up the tissue and spun the samples briefly in a centrifuge to remove the larger debris. Then we injected a tiny amount of the extract into the brains of young transgenic mice.

The results were positive. Three to five months later, before the mice would normally start generating their own Aβ plaques, substantial aggregated Aβ appeared in the brains of mice that received the Alzheimer's brain extracts. The degree of Aβ plaque formation was proportional to the amount of Aβ in the donor brain extract and to how long it had to incubate—patterns you would expect to see if the extracts caused the plaques. Most crucially, donor brains lacking aggregated Aβ did not seed plaque formation in the transgenic mice.

DEFINING THE Aβ SEED

ALTHOUGH THESE EXPERIMENTS showed that Aβ deposition could be initiated by Alzheimer's brain extracts, they did not definitively indicate that Aβ in the extracts accounted for the plaques. That uncertainty compelled us to address several additional questions. First, we asked whether the Aβ deposits that we saw in the mice were merely the material that was injected. Here the answer was no: one week later no evidence could be found of aggregated Aβ in the brain. Rather plaques became apparent only after a lag of a month or more.

Second, we considered the possibility that plaque formation was stimulated by some component of the human brain extract besides the Aβ, perhaps a human virus. We ruled out this prospect by confirming that brain extracts from aged but pathogen-free APP-transgenic mice can seed as effectively as human brain extracts, as long as the samples contain ample aggregated Aβ. In addition, because extracts from non-Alzheimer's brains did not cause Aβ clumping, we could eliminate the possibility that the plaques were just a response to brain injury incurred during the process of delivering the extract.

Although the evidence now strongly pointed to Aβ as the culprit, we wanted more direct proof. Our third step was to remove Aβ from the brain extracts using antibodies that selectively mop up Aβ. This simple procedure abolished the ability of the Alzheimer's brain samples to induce plaque formation. Finally, when we used a strong acid to make the misfolded proteins unfold, the brain extracts failed to induce plaque formation. We thus confirmed that the shape of the protein governs its ability to induce the misfolding and aggregation of other Aβ molecules.

We were now reasonably certain that misfolded Aβ was the active seeding agent in the brain samples, but a key piece of the puzzle remained elusive. If aggregated Aβ alone is the seed, it should be possible to induce plaques using Aβ that is synthesized and made to clump in a test tube in the absence of the many other substances in the brain. We knew that seeding with synthetic proteins might be challenging because studies with prions had shown that laboratory material can differ in subtle but apparently important ways from that taken directly from the brain.

With this caveat in mind, we injected various forms of synthetic, aggregated Aβ into APP-transgenic mice, then waited out the usual incubation period of three to five months. The results were disappointing; no obvious initiation of plaque formation was apparent in this time frame. But Prusiner, Jan Stöhr, Kurt Giles and their collaborators at U.C.S.F. injected synthetic Aβ fibers into the brains of APP-transgenic mice, and after a prolonged incubation period of more than six months, the mice showed clear evidence of seeded Aβ deposition in the brain. Although the synthetic seeds proved less potent than naturally generated Aβ seeds, the

© 2015 Scientific American

findings provide a persuasive demonstration that pure, aggregated Aβ alone, in the absence of other factors, is able to stimulate the formation of Aβ deposits in the brain.

In more recent experiments, we have begun to investigate the features of Aβ seeds that enable them to promote protein clumping in the brain. Because most of the Aβ protein in the seeding extracts is contained in the long, insoluble fibers, we expected that these fibers would be the most effective seeds. The results surprised us. By spinning the brain extracts at high speed in a centrifuge, we divided the Aβ-rich brain extracts into two components: an insoluble pellet containing mostly Aβ fibers at the bottom of the centrifuge tube and a clear liquid above the pellet containing very small, soluble forms of the Aβ protein. As anticipated, the vast majority of the Aβ settled into the pellet, which, when broken up and injected into the brains of transgenic mice, induced Aβ aggregation as effectively as did the whole-brain extract. Unexpectedly, though, the soluble portion also strongly induced Aβ aggregation and plaque formation, despite containing less than one one-thousandth as much Aβ as the pellet fraction. What is more, the soluble seeds were readily destroyed by an enzyme, proteinase K, whereas the insoluble seeds were not.

There is good news and bad news in the variable size and fragility of Aβ seeds. The bad news is that small, soluble assemblies, which can move through the brain with greater ease than the larger fibers, are particularly potent seeds. On the other hand, their sensitivity to proteinase K hints that soluble seeds might be especially amenable to treatments designed to eliminate them from the brain. Also, being soluble, the small seeds might be readily detectable in bodily fluids and so might serve as molecular sentinels for the early diagnosis of Alzheimer's, possibly well before the onset of dementia. Because protein seeding appears to begin at the very earliest stages of the disease, having a way to detect and neutralize those seeds could go a long way toward preventing brain damage and dementia.

BEYOND ALZHEIMER'S

NATURE SELDOM MISSES an opportunity to exploit a mechanism for multiple purposes, and seeded protein aggregation is no exception. It turns up not only in disease, but it can also transmit biological information in beneficial processes. In the 1990s, for instance, Reed Wickner of the NIH proposed that some fungal proteins use this strategy to aid in cell survival, a postulate that now has been confirmed in numerous labs. Moreover, Susan Lindquist of the Massachusetts Institute of Technology and Eric R. Kandel of Columbia University have championed the intriguing hypothesis that the prionlike propagation of specific proteins helps to stabilize brain circuits, thereby acting to preserve long-term memories.

So far, however, the lion's share of the research points to a role for seeded protein aggregation in disease. Proteins whose seeded aggregation has been implicated in brain disorders include α-synuclein (in Parkinson's), superoxide dismutase-1 (in ALS), TDP-43 (in ALS and frontotemporal dementia), huntingtin (in Huntington's disease) and tau (in a number of neurodegenerative diseases). Many other neurodegenerative diseases involve protein aggregation, and it will be important to see whether the seeding principle applies to them as well.

In other developments, investigators have discovered that some proteins involved in the regulation of gene function include a prionlike domain—that is, a stretch of amino acids that enables a protein to induce its same structure in like molecules. By their nature, these proteins tend to aggregate, a proclivity that can be augmented by certain mutations. A research team led by J. Paul Taylor of St. Jude Children's Research Hospital in Memphis and James Shorter of the University of Pennsylvania has reported that mutations in the prionlike domains of nucleic acid–binding proteins called hnRNPA2B1 and hnRNPA1 cause multisystem proteinopathy, a complex malady affecting the nervous system, muscle and bone. Moreover, seeded aggregation has been demonstrated experimentally for other proteins that cause conditions outside the nervous system, such as certain amyloidoses and some forms of cancer—and the spectrum of disorders involving prionlike propagation of proteins may continue to grow.

If therapies are to emerge from our growing understanding of the seeding concept, we must establish how misfolded proteins injure cells and tissues; such information could help block damage even if halting unwanted protein aggregation itself proves difficult. Research shows that aggregated proteins can disable cells in many ways, including causing toxic interactions of the aggregates with a cell's components or disrupting the normal function of biomolecules. At the same time, we must understand more fully how pathogenic proteins arise and break down and the conditions under which they misfold and form seeds. Further insights into the progression of disease will also certainly come from clarifying how cells take up, transport and release protein seeds. Finally, a critical open question is why growing old so strongly increases the risk for neurodegenerative diseases. Answers to these questions could suggest new ways to defang pathogenic proteins.

The weight of evidence increasingly favors the once unorthodox notion that a simple change in shape can transform a protein from friend to foe. In his Nobel Prize lecture describing the discovery of prions, Prusiner predicted that the basic process by which prions involved in mad cow and related illnesses impose their toxic features on normal proteins would be found to operate in other degenerative diseases. The dawn of the 21st century has witnessed the experimental confirmation of this prediction. Indeed, prionlike seeded protein aggregation may explain the origin of some of the most feared diseases of old age—and provide a compelling conceptual framework that may one day translate into treatments that alter the relentless progression of neurodegenerative illnesses. SA

Lary C. Walker is a research professor at the Yerkes National Primate Research Center and associate professor of neurology at Emory University. **Mathias Jucker** is a research professor at the Hertie Institute for Clinical Brain Research at the University of Tübingen in Germany and at the German Center for Neurodegenerative Diseases, also in Tübingen. The authors have collaborated extensively over the past two decades on research into brain aging and Alzheimer's disease.

MORE TO EXPLORE

Self-Propagation of Pathogenic Protein Aggregates in Neurodegenerative Diseases. Mathias Jucker and Lary C. Walker in *Nature*, Vol. 501, pages 45–51; September 5, 2013.

Cell-to-Cell Transmission of Pathogenic Proteins in Neurodegenerative Diseases. Jing L. Guo and Virginia M. Y. Lee in *Nature Medicine*, Vol. 20, No. 2, pages 130–138; February 2014.

scientificamerican.com/magazine/sa

© 2015 Scientific American

GERIATRICS

THE OLDEST OLD

People in their late 90s or older are often healthier and more robust than those 20 years younger. Traditional views of aging may need rethinking

By Thomas T. Perls

IN MEDICAL SCHOOL I WAS TAUGHT THAT THE INCIDENCE OF CHRONIC, DISABLING DISORDERS, particularly Alzheimer's disease, increases inexorably with age. I therefore expected that people older than 95 years, often called the oldest old, would be my most debilitated patients. Yet when I became a fellow in geriatrics, I was surprised to find that the oldest old were often the most healthy and agile of the senior people under my care. In fact, the morning I was scheduled to interview a 100-year-old man as part of a research project, he told me we would have to delay the visit. He had seen 19 American presidents take office, and he would be busy that morning voting for the next one.

IN BRIEF

Although our physical and mental health tends to deteriorate as we age, this process does not occur at the same pace in everyone. People more than 95 years of age—the oldest old—are often healthier than people who are decades younger.

Men who survive into their 90s appear to have better physical and mental functioning than women of the same age, a phenomenon called gender crossover.

Some individuals may be well suited for long-term survival because they possess genetic combinations that protect them against damaging biological processes and environmental exposures.

Because the longest-lived people often have few infirmities until shortly before death, caring for an aging population may not be as expensive as feared.

JEREMY SUTTON-HIBBERT *Alamy*

© 2015 Scientific American

HURLING STRONGLY
in a photograph taken at age 102, Takashi Shimokawara still holds world records in the men's over-100 class for discus and javelin throwing. He died at age 104, a victim not of old age but of the earthquake and tsunami that struck Japan in 2011. Shimokawara was among the many healthy centenarians who contradict the traditional idea that age always brings with it severe debilitation.

© 2015 Scientific American

Such encounters made me wonder if the prevailing view of aging as advancing infirmity was partly wrong. Could it be that many people in their upper 90s enjoy good health and that the oldest old constitute a special—and long-misunderstood—population? Since then, the centenarians I have met have, with few exceptions, reported that their 90s were essentially problem-free. As nonagenarians, many were socially engaged and enjoyed the outdoors and the arts. They basically carried on as if age were not an issue. And accumulating evidence indicates that a significant number of the oldest old are indeed healthier than many people in their 80s or early 90s. The common idea that advancing age inevitably leads to extreme deterioration does, indeed, seem to require revision.

Estimated costs of caring for the oldest old in the future might need modification as well. The centenarian population grew by 66 percent in the U.S. from 1980 to 2010. Many demographers predict that 20 million to 40 million people will be aged 85 or older in the year 2040 and that 500,000 to four million will be centenarians in 2050. The economic burden of caring for people older than 85 could be vast, especially if a huge percentage of them need special care. Yet it may well be that health bills for the oldest old will be lower than previously expected.

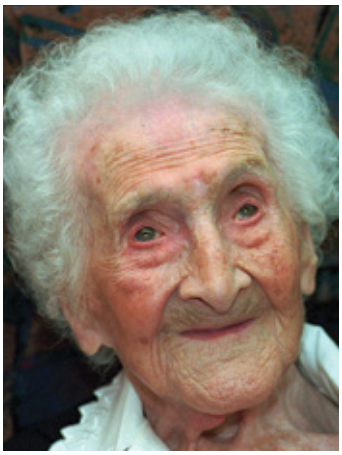
Some of the first evidence supporting my suspicions came from a study on Alzheimer's disease that I conducted with my mentor, Lewis A. Lipsitz of the Hebrew Rehabilitation Center in Boston. Surveys reported that this disorder devastates the mind and ultimately kills about 40 percent of those aged 85 and older. Some investigators believe that close to 50 percent of 90-year-olds have Alzheimer's disease and that up to 70 percent of centenarians are affected. Many of the studies on which these conclusions are based, however, did not include subjects older than 93 years, which casts some doubt on these projections. In 1991 Lipsitz and I undertook a pilot study to determine whether the occurrence of Alzheimer's at the center, a chronic care hospital, matched the predictions for centenarians. We found that of the 12 residents in their 100s, only four seemed to have Alzheimer's. This low figure—only 33 percent—was particularly striking considering that residents of such facilities are more likely to be impaired than are their counterparts in the community.

MORTALITY TRENDS

Life Begins at 97

JEANNE CALMENT, a Frenchwoman who lived to age 122, died in 1997. She survived longer than anyone whose age has been confirmed. Calment is among the people who taught researchers that mortality rates for the oldest old are much lower than would be predicted by extrapolating from the death rates of younger individuals (*left graph, opposite page*). James W. Vaupel of the Max Planck Institute for Demographic Research in Rostock, Germany, Anatoli Yashin, now at Duke University, A. Roger Thatcher, formerly at the Office of Population Censuses and Surveys in London, and Vaino Kannisto, formerly at the United Nations, examined death statistics for eight million people. They found that after age 97 a person's chance of dying at a given age veers from the expected trend (*light green in graph at upper left, opposite page*). Instead of increasing exponentially, the rate slows to become more linear (*dark green*). (The ratio would exceed 1 if an entire age group were to die in less than a year.) These findings support the author's suggestion that the oldest members of our species tend to be healthier than expected.

Similar mortality trends were observed in medflies (*lower left graph, opposite page*). James R. Carey of the University of California, Davis, compared expected death rates (*light orange*) with observed rates (*dark orange*). He found that the chance of dying at any given age peaked at around the age of 50 days. After that, risk declined, so by 100 days, the oldest insects had only a 5 percent chance of dying on a given day.



Record holder at her 120th birthday party.

FRANCOIS MORI *AP Photo*

SELECTIVE SURVIVAL

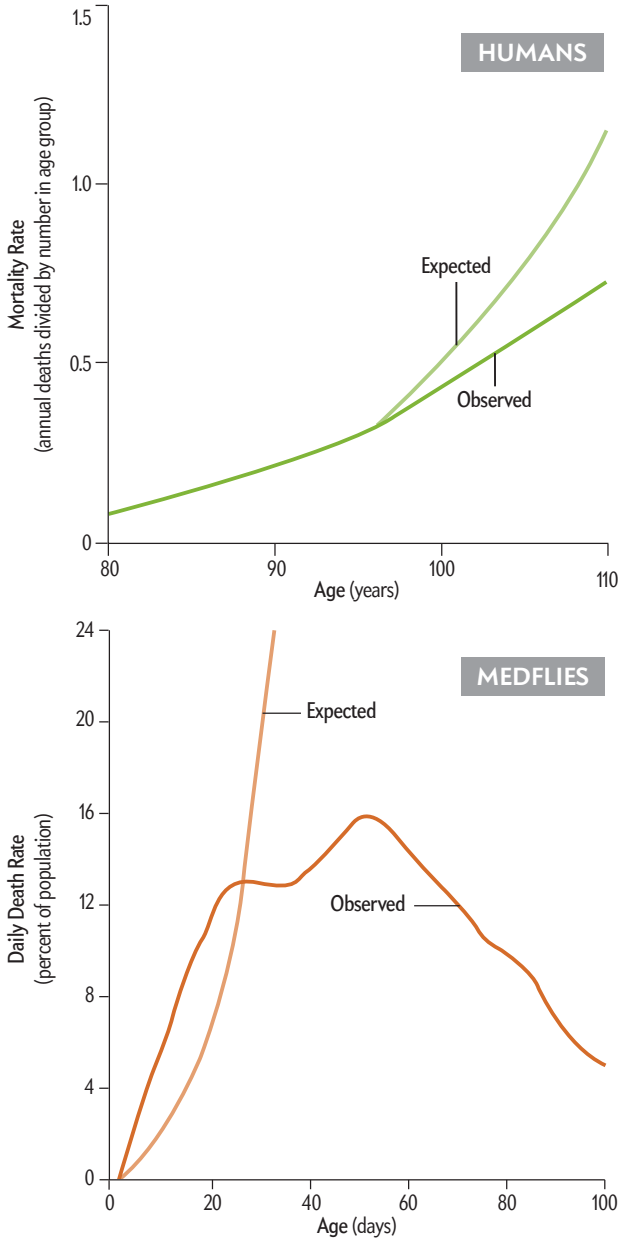
OUR FINDING SUGGESTED that, at least cognitively, the oldest old are in better shape than has usually been assumed. What, we wondered, could explain their good condition? We suspect that the answer to this riddle is that, for whatever reason, some people are particularly resistant to acquiring the disorders that disable and kill most people before age 90. Because of this resistance, they not only outlive others, they do so relatively free of disabilities. In a kind of survival-of-the-fittest phenomenon, these individuals seem to be selected for long-term survival because they possess traits that enable them to avoid or delay killer diseases that commonly accompany aging. And if they do incur illnesses, they are better able to deal with them.

The concept of selective survival was applied, somewhat more narrowly, by demographers in the 1970s to older African-American populations. Researchers reported that although the death rates for blacks were higher than for whites in the U.S. up to age 75, the trend reversed after that age. Then, in what some called a crossover phenomenon, whites were more likely to die at a given age than their African-American counterparts were. They speculated that blacks tended to die earlier because more of them were economically disadvantaged and had less access to health care services. Therefore, those who survived represented an unusually vigorous group, able to overcome obstacles that defeated others. Their vigor, in turn, later gave them a survival advantage.

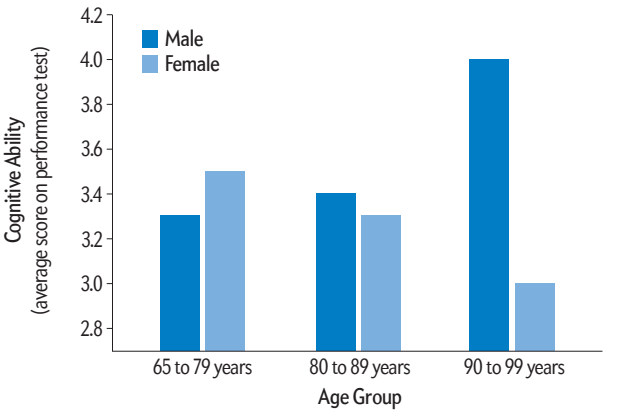
This selective survival hypothesis may also clarify various other once puzzling findings demonstrating unusually good cognitive and physical health in the oldest old. It seems that men who survive into their late 80s become less and less likely to develop Alzheimer's with each passing year. Moreover, the average man in his late 90s has a more intact mind than the average man in his 80s. These patterns prob-

© 2015 Scientific American

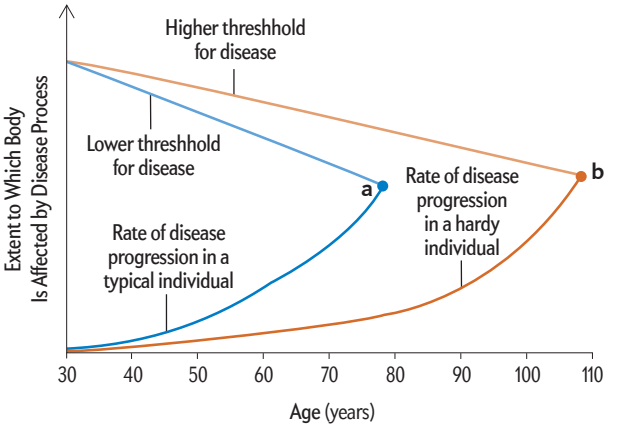
Death-Defying Statistics



COMMON SENSE suggests that the death rate for humans (*top*) should skyrocket after age 97; instead it continues to climb slowly. For medflies (*bottom*), the death rate actually declines after the ripe old age of 50 days, making the oldest old less likely to die than their younger counterparts.



COGNITIVE ABILITIES of oldest old men (*dark blue bar at far right*) are on average higher than the abilities of their female peers even though among people aged 65 to 79, women seem to have a slight advantage. The reversal, known as a gender crossover, occurs between the ages of 80 and 89. It arises because men who are cognitively impaired generally die earlier than do women, leaving mainly mentally intact men who live on.



HIGH THRESHOLD for acquiring chronic diseases and a slower aging process may help explain why the oldest old often survive in good health, according to the author's theoretical model. In most people, tissue damage resulting from disease processes occurs relatively rapidly (*dark blue*). Also, their disease threshold becomes lower quickly with age (*light blue*), so the symptoms of age-related diseases appear by about age 80 (*a*). Hardy individuals who age slowly (*dark orange*) and have a higher threshold for disease (*light orange*) become symptomatic much later (*b*), if at all.

ably emerge because men who are susceptible to Alzheimer's generally die of the condition in their 80s or early 90s. These trends would be explained if the group of men who reach their late 90s consist almost exclusively of individuals who are not susceptible to Alzheimer's and who therefore retain their cognitive abilities indefinitely. More study should reveal whether this is the case.

GENDER CROSSOVER

SURPRISINGLY, AS A GROUP, men older than 90 generally have better mental function than their female peers do. Women with dementia, it seems, tend to live with their illness rather than die from it. As a consequence, very old women on average retain less of their mental abilities than do men of the same age—who represent the healthy survivors left after other

LISA BURNETT

© 2015 Scientific American

THREE WHO THRIVED

Plenty of Sushi and Sleep

Research suggests that good genes probably provide the best hope for a long and healthy life. Other factors may be important, however. The people shown here had their own hypotheses to explain their longevity; further scientific studies should help clarify the issue.

GERTRUDE WEAVER (*left*) one day before her 116th birthday and nearly a century after her marriage at age 17. She is the oldest living American, according to the Gerontology Research Group. Weaver enjoys manicures, wheelchair dancing and Bible study. She says the secret to a long life is trusting God and being kind to others. WALTER BREUNING (*center*) at age 114, when he was the world's oldest living man and a member of the author's study of centenarians. Breuning, who dressed in a suit and tie every day, attributed his longevity to staying mentally and physically active (he did not retire until age 99) and to his diet: a hearty breakfast and lunch but only fruit snacks in the evening. MISAO OKAWA (*right*) at age 115, posing for a photograph on March 3, 2014—a day known in Japan as the Doll's Festival—about a year after Guinness World Records recognized her as the world's oldest living person. What keeps her going? Three large meals a day (sushi is a favorite) and getting at least eight hours of sleep a night. Also, she told *The Telegraph,* "You have to learn to relax."

men susceptible to dementia have died off.

At later ages, men also do better than women in terms of physical health. Men in their 60s and 70s are more susceptible than are women to strokes and heart attacks. Delayed onset of these acute conditions allows women to survive longer than men. In absolute numbers, many more women are still alive at 95, but in terms of average health, men begin to take the lead. This switch to more mentally and physically fit men after age 90 is called a gender crossover.

Early signs of the gender crossover can be seen in studies of 80-year-olds. Men who survive to this age without major health problems often continue to live without needing special care. Richard M. Suzman and his colleagues at the National Institute on Aging found that men older than 80 years in one such study were more independent than were similarly aged women. Their report indicated that 44 percent of the men in that age group were robust and independent compared with only 28 percent of women. Additionally, Kenneth G. Manton and Eric Stallard of Duke University estimated the active life expectancy—that is, the years of independent life left—for members of the U.S. senior population. Their findings showed that after age 85, men could expect to live a healthy and active life longer than women could.

What biological and environmental factors might allow the oldest old humans to reach age 95 and beyond in good health? Multiple and intertwined influences undoubtedly play important roles. So-called longevity genes seem to protect against the development of diseases; genetically or otherwise determined adaptive abilities enable survivors to avoid potentially life-threatening conditions. Modifications in everyday activities, such as not smoking, practicing better nutrition and exercising, may also help some people stay fit longer. Basic good luck surely helps as well.

THE GENETIC FACTOR

TEMPTING CANDIDATES for possible longevity genes in humans are ones that control the body's mechanism for protecting itself against oxygen radicals. These naturally occurring, highly reactive compounds damage DNA and can destroy cells. Everyone has a genetically determined ability to combat this type of damage. Gene variants that give rise to unusually efficient resistance to oxidative damage could well contribute to the life span of the oldest old by slowing the rate at which oxygen radicals damage cells. Other gene candidates include those that repair aging-related damage to DNA or modulate cells' efficiency to produce and use energy.

What is clear, though, is that there is not just one gene or magic bullet responsible for a centenarian's survival advantage. What makes centenarians rare is that they have just the right combinations of likely hundreds of genetic variants that enhance their abilities to age slowly and decrease their risk for age-related diseases. Making matters even more complicated, there are probably many winning combinations associated with different ethnicities and environments. We are encouraged by the fact that a few combinations have an accura-

AP PHOTO (*left*); JOHN MOORE *Getty Images* (*center*); AP PHOTO (*right*)

© 2015 Scientific American

cy of more than 80 percent in differentiating centenarians beyond the age of 106 from noncentenarians. This accuracy is consistent with our hypothesis that the influence of genes on survival becomes stronger and stronger with older and older ages beyond 100 years.

Until recently, scientists thought that centenarians not only have genes that protect against biological processes and environmental exposures conducive to aging but also lack genetic variants associated with increased risk of age-related diseases. Three different studies have now shown, however, that centenarians appear to have just as many of the "bad" variants as the general population. Perhaps a key role of the protective variants is to trump these disease-associated variants.

A notable exception is a variant of the gene coding for the protein apolipoprotein E (*APOE*) that has been tied to a substantially increased risk of acquiring Alzheimer's. There are three common variants: e2, e3 and e4. People who inherit two e4 genes (one from each parent) have eight times as great a risk as the general population of developing the disease, and those who acquire the disease display symptoms at an average age of 68. Alzheimer's patients with two e3 genes demonstrate symptoms of the disease somewhat later, at about 75 years. The role of e2 remains unclear, but there is evidence that it is associated with a lower risk of developing Alzheimer's. As it turns out, the frequency of the e4 variant is very low among centenarians, most likely because it is so strongly associated with Alzheimer's, vascular disease and premature mortality.

Genes may provide the blueprint for how long a person might live. In effect, they can be considered indicators of how well a person can cope with disease. As such, genes help to determine two interrelated properties that influence aging: adaptive capacity and functional reserve. Adaptive capacity is a person's ability to overcome a disease or injury or to cope with such stresses effectively. Functional reserve refers to how much of an organ is required for its adequate performance. Obviously, one's adaptive capacity depends in part on the body's functional reserve because the ability to deal with disease requires the proper functioning of organs.

The importance of these two characteristics to the survival of many oldest old can be seen in the varying effects that the buildup of neurofibrillary tangles has on cognition. Neurofibrillary tangles describe the web of dead brain cells that occur naturally with aging but appear in abundance in patients with Alzheimer's. The number of tangles that can accumulate before signs of Alzheimer's emerge varies. For example, an autopsy revealed that a 103-year-old man who displayed few outward signs of Alzheimer's had a level of neurofibrillary tangles that in a younger brain would indicate the patient was probably demented. Presumably, the older man had an excess reserve of brain function that allowed him to compensate for the process that was damaging his brain. Perhaps people who have a slow buildup of tangles and a high tolerance for them can remain mentally intact for a long time, showing overt signs of Alzheimer's only very late in life, if at all.

NEW THOUGHTS ON AGING

THE DISCOVERY that many people older than 95 are in good shape may mean that future planning for the health care of the oldest old will need to be revised. Much of that planning is based on the theory that although lethal conditions might be postponed as medical technology improves, the incidence of degenerative diseases will be unaltered. The theory predicts that the oldest old will keep suffering from more disease and chronic disability than people in their 80s do. If this theory were true, then the continued increase in the size of the oldest old population would portend a significant burden of poor health and quality of life among the oldest members of our society.

The emerging data, however, fit better with an opposing theory. James F. Fries of Stanford University has proposed that healthier ways of life and medical advances will compress morbidity, mortality and disability into a shorter time period. Thus, the onset both of major fatal diseases (heart disease, cancer, stroke and Alzheimer's) and of age-associated debilitating diseases (degenerative joint disease, sensory impairments and benign memory loss) would be postponed.

Consistent with Fries's hypothesis, robust centenarians often have a relatively short period of infirmity before death. Supercentenarians, a term for people who live to 110 years and beyond, are extremely rare. Yet the New England Centenarian Study has enrolled enough of these "super agers" to demonstrate that, on average, they spend only the last five years of their exceptionally long lives with demonstrable disease or disability.

Jeanne Calment of Arles, France, died at age 122 in August 1997, making her the longest living person ever. Most of us with Methuselean aspirations, in contrast, are up against incredible odds. But recent research on the oldest old has prompted new thinking about the biology of aging. Genetic, biochemical and epidemiological studies should reveal why some people possess resistance to debilitating conditions—and may offer ways to increase that ability in a broader swath of the population. Further, to our relief, the research implies that as the oldest old become more numerous, they may not become a massive drain on the economy. Counter to prevalent theories of aging, many people in their late 90s or 100s lead active, healthy lives. If they represent a survival-of-the-fittest cohort, the time may have come to abandon our past perceptions of our oldest citizens. SA

Thomas T. Perls met his first centenarian in his own family: his great-grandmother, Julia Grunewald, lived to be 102. As principal investigator of the New England Centenarian Study, Perls examines definitions of normal aging and underlying determinants of exceptional longevity. He received his medical degree from the University of Rochester and his master's in public health from Harvard University. Perls is a professor of medicine at Boston University School of Medicine and a geriatrician at Boston Medical Center.

MORE TO EXPLORE

Living to 100: Lessons in Living to Your Maximum Potential at Any Age. Thomas T. Perls, Margery Hutter Silver and John F. Lauerman. Basic Books, 1999.

Biodemography of Human Ageing. James W. Vaupel in *Nature,* Vol. 464, pages 536–542; March 25, 2010.

Health Span Approximates Life Span amongst Many Supercentenarians: Compression of Morbidity at the Approximate Limit of Life Span. Stacy L. Andersen, Paola Sebastiani, Daniel A. Dworkis, Lori Feldman and Thomas T. Perls in *Journal of Gerontology: Biological Sciences,* Vol. 67A, No. 4, pages 395–405; January 4, 2012.

Genetic Signatures of Exceptional Longevity in Humans. Paola Sebastiani et al. in *PLOS ONE,* Vol. 7, No. 1, e29848; January 18, 2012.

© 2015 Scientific American

© 2015 Scientific American

FAST-FORWARD

IF HUMANS WERE BUILT TO LAST

We would look a lot different if evolution had designed the human body to function smoothly for a century or more

By S. Jay Olshansky, Bruce A. Carnes and Robert N. Butler

BULGING DISKS, FRAGILE BONES, FRACTURED HIPS, TORN ligaments, varicose veins, cataracts, hearing loss, hernias and hemorrhoids: the list of bodily malfunctions that plague us as we age is long and all too familiar. Why do we fall apart just as we reach what should be the prime of life?

The living machines we call our bodies deteriorate because they were not designed for extended operation and because we now push them to function long past their warranty period. The human body is artistically beautiful and worthy of all the wonder and amazement it evokes. But from an engineer's perspective, it is a complex network of bones, muscles, tendons, valves and joints that are directly analogous to the fallible pulleys, pumps, levers and hinges in machines. As we plunge further into our postreproductive years, our joints and other anatomical features that serve us well or cause no problems at younger ages reveal their imperfections. They wear out or otherwise contribute to the health problems that become common in the later years.

In evolutionary terms, we harbor flaws because natural selection, the force that molds our genetically controlled traits, does not aim for perfection or endless good health. If a body plan allows individuals to survive long enough to reproduce (and, in humans and various other organisms, to raise their young), then that plan will be selected. That is, individuals robust enough to reproduce will pass their genes—and therefore their body design—to the next generation. Designs that seriously hamper survival in youth will be weeded out (selected against) because most affected individuals will die before having a chance to produce offspring. More important, anatomical and physiological quirks that become disabling only after someone has reproduced will spread. For example, if a body plan leads to total collapse at age 50 but does not interfere with earlier reproduction, the arrangement will get passed along despite the harmful consequences late in life.

Had we been crafted for extended operation, we would have fewer flaws capable of making us miserable in our later days. Evolution does not work that way, however. Instead it cobbles together new features by tinkering with existing ones in a way that would have made Rube Goldberg proud.

The upright posture of humans is a case in point. It was adapted from a body plan that had mammals walking on all fours. This tinkering undoubtedly aided our early hominid ancestors: standing on our own two feet is thought to have promoted everything from food gathering and tool use to enhanced intelligence. Our backbone has since adapted somewhat to the awkward change: the lower vertebrae have grown bigger to cope with the increased vertical pressure, and our spine has curved a bit to keep us from toppling over. Yet these fixes do not ward off an array of problems that arise from our bipedal stance.

WHAT IF?

THE THREE OF US have pondered what the human body would look like had it been constructed specifically for a healthy long life. The anatomical revisions depicted on these pages are fanciful and incomplete. Nevertheless, we present them to draw attention to a serious point. Aging is frequently described as a disease that can be reversed or eliminated. Indeed, many purveyors of youth-in-a-bottle would have us believe that the medical problems associated with aging are our own fault, arising primarily from our decadent lifestyles. Certainly any fool can shorten his or her life. But it is grossly unfair to blame people for the health consequences of inheriting a body that lacks perfect maintenance and repair systems and was not built for extended use or perpetual health. Our bodies would still wear out over time even if some mythical, ideal lifestyle could be identified and adopted.

IN BRIEF

The process of human evolution has resulted in bodies that are optimized for successful reproduction and child-rearing but are not necessarily designed for healthy, long lives.

Medical problems associated with aging are often described as diseases that are our own fault, but it is unfair to blame people for inheriting bodies that were not designed for extended use. We can shorten our lives, but not prolong them indefinitely.

If humans were built primarily for longevity and perpetual health, our anatomies and even our bodies' molecular processes would look very different than they currently do.

The single-minded pursuit of life extension could actually be harmful to our species' long-term survival.

Illustrations by Patricia J. Wynne

© 2015 Scientific American

This reality means that aging and many of its accompanying disorders are neither unnatural nor avoidable. No simple interventions can make up for the countless imperfections that permeate our anatomy and are revealed by the passage of time. We are confident, however, that researchers will be able to ease some of the maladies of aging. Investigators are rapidly identifying (and discerning the function of) our myriad genes, developing pharmaceuticals to control them, and learning how to harness and enhance the extraordinary repair capabilities that already exist inside our bodies. These profound advances will eventually help compensate for many of the design flaws contained within us all.

HEALTH AND LONGEVITY

OUR RESEARCH INTEREST in redesigning the *Homo sapiens* body is a reaction to the health and mortality consequences of growing old. We focus on anatomical "oddities" and "design flaws" not only because they would be familiar to most readers, but because they represent a small sample of lethal and disabling conditions that threaten the length and quality of life. It is important to recognize that we live in a world in which human ingenuity has made it possible for an unprecedented number of people to grow old. Our redesign goal is thus to draw attention to the health consequences associated with the aging of individuals and populations.

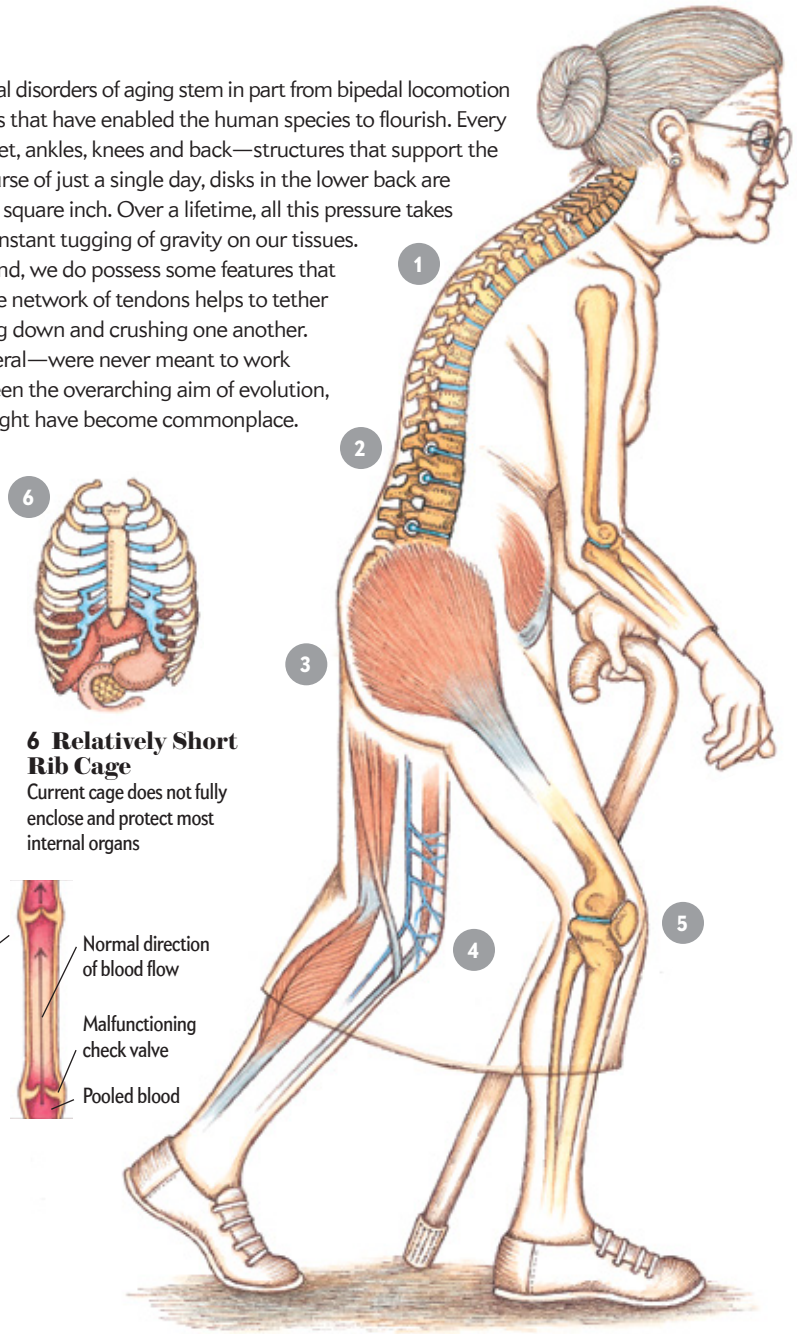
ANATOMY LESSON 1

Walk This Way

A number of the debilitating and even some of the fatal disorders of aging stem in part from bipedal locomotion and an upright posture—ironically, the same features that have enabled the human species to flourish. Every step we take places extraordinary pressure on our feet, ankles, knees and back—structures that support the weight of the whole body above them. Over the course of just a single day, disks in the lower back are subjected to pressures equivalent to several tons per square inch. Over a lifetime, all this pressure takes its toll, as does repetitive use of our joints and the constant tugging of gravity on our tissues.

Although gravity tends to bring us down in the end, we do possess some features that combat its ever present pull. For instance, an intricate network of tendons helps to tether our organs to the spine, keeping them from slumping down and crushing one another.

But these anatomical fixes—like the body in general—were never meant to work forever. Had longevity and persistent good health been the overarching aim of evolution, arrangements such as those depicted at the right might have become commonplace.



FLAWS

1 Bones That Lose Minerals after Age 30
Demineralization makes bones susceptible to fractures and, in extreme cases, can cause osteoporosis (severe bone degeneration), curvature of the spine and "dowager's hump"

2 Fallible Spinal Disks
Years of pressure on the spongy disks that separate the vertebrae can cause them to slip, rupture or bulge; then they, or the vertebrae themselves, can press painfully on nerves

3 Muscles That Lose Mass and Tone
Such atrophy can impede all activities, including walking. In the abdomen, hernias can arise as the intestines (always pulled by gravity) protrude through weak spots in the abdominal wall. Flaccid abdominal muscles also contribute to lower-back pain

4 Leg Veins Prone to Varicosity
Veins (*right*) become enlarged and twisted when small valves that should snap shut between heartbeats (to keep blood moving up toward the heart) malfunction, causing blood to pool. Severe varicosities can lead to swelling and pain and, on rare occasions, to life-threatening blood clots

5 Joints That Wear
As joints are used repetitively through the years, their lubricants can grow thin, causing the bones to grind against one another. The resulting pain may be exacerbated by osteoarthritis and other inflammatory disorders

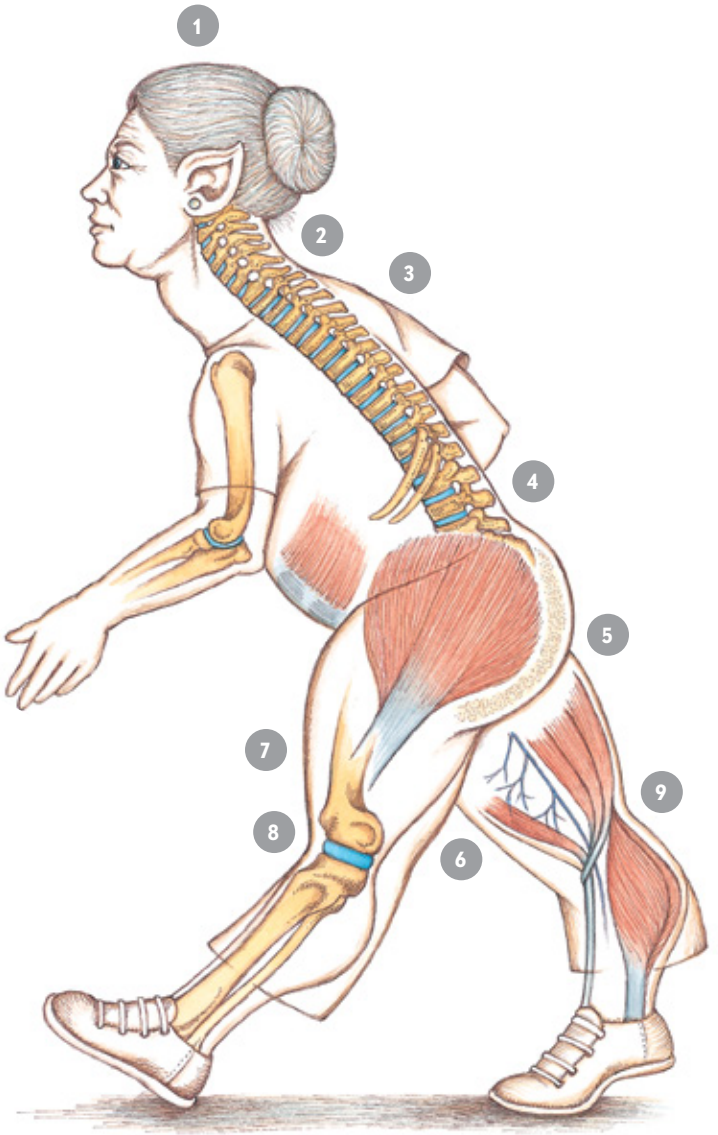
6 Relatively Short Rib Cage
Current cage does not fully enclose and protect most internal organs

© 2015 Scientific American

Even the term "flaw" requires clarification. Living things, and everything they make, eventually fail. The cause of failure is a flaw only when the failure is premature. A race car that fails beyond the end of the race has no engineering flaws. In the same way, bodies that fail in the postreproductive span of life may contain numerous design oddities, but they have no design flaws as far as evolution goes.

There are countless other aspects of human biology that would merit modification if health and longevity were nature's primary objective. For example, gerontologists theorize that aging is caused, in part, by a combination of the molecular damage that inevitably arises from operating the machinery of life within cells and the imperfect mechanisms for molecular surveillance, maintenance and repair that permit damage to accumulate over time. If this view of the aging process is correct, then modifying these molecular processes to lessen the severity or accumulation of damage, or to enhance the maintenance and repair processes, should have a beneficial impact on health and longevity. These wondrous modifications, however, would have little effect unless the common sense that is needed to avoid destructive lifestyles becomes more widespread among people.

Living things are exceedingly complex, and experience teaches



FIXES

1 Shorter Stature
Would provide a lower center of gravity, perhaps preventing the falls that often fracture demineralized bones

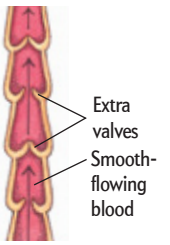
2 Curved Neck with Enlarged Vertebrae
Would counterbalance the tilted torso and enable the head to stay up and face forward

3 Forward-Tilting Upper Torso
Would relieve pressure on vertebrae, thereby lessening the risk of ruptured or slipped disks, which contribute, along with weakening abdominal muscles, to lower-back pain

4 Thicker Disks
Would resist destructive pressures

5 Extra Muscles and Fat
Would add weight on the bones, which would help counter the effects of demineralization; they would also cushion bones against breakage during falls

6 Leg Veins with More Check Valves
Would combat the development of varicose veins

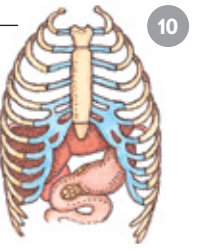


7 Thicker Bones
Would protect against breakage during falls

8 Knee Able to Bend Backward
Would make the bones less likely to grind and deteriorate, especially if the knee never locked in place. But the absence of a locking mechanism would make it hard to stand for very long, so further modifications would be needed

9 Larger Hamstrings and Tendons
Would help support the leg and hip

10 Cage with Added Ribs
Could help prevent hernias and other problems by holding organs in place more effectively



© 2015 Scientific American

ANATOMY LESSON 2

Plan a Head

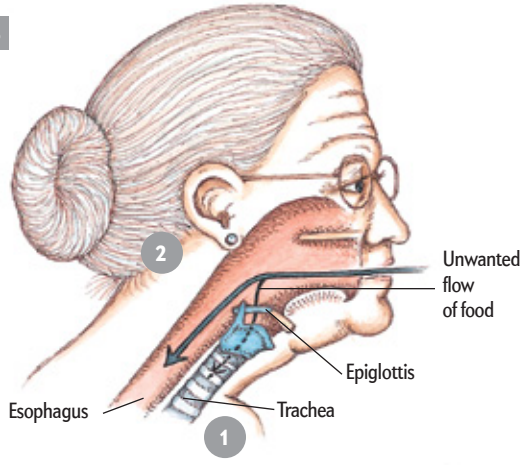
Various parts of the head and neck become problematic with disturbing regularity as people age. Consider the eye: the human version is an evolutionary marvel, but its complexity provides many opportunities for things to go wrong over a long lifetime.

Our vision diminishes as the protective fluid of the cornea becomes less transparent over time. The muscles that control the opening of the iris and the focusing of the lens atrophy and lose responsiveness, and the lens thickens and yellows, impairing visual acuity and color perception. Further, the retina—responsible for transmitting images to the brain—can detach fairly easily from the back of the eye, leading to blindness.

Many of those problems would be difficult to design away, but the squid eye suggests an arrangement that could have reduced the likelihood of retinal detachment. A few anatomical tweaks could also have preserved hearing in the elderly.

Suboptimal design of the upper respiratory and digestive systems makes choking another risk for older people. A simple rearrangement would have fixed that problem, albeit at the cost of severe trade-offs.

FLAWS

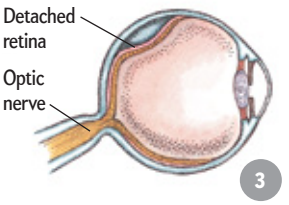


1 Common Upper Passageway for Food and Air

When food travels toward the esophagus, a flaplike tab of cartilage (the epiglottis) closes off the trachea, or windpipe. With age, a progressive loss of muscle tone decreases the tightness of the seal, raising the risk of inhaling food or drink

2 Ear with Fragile Transmitters

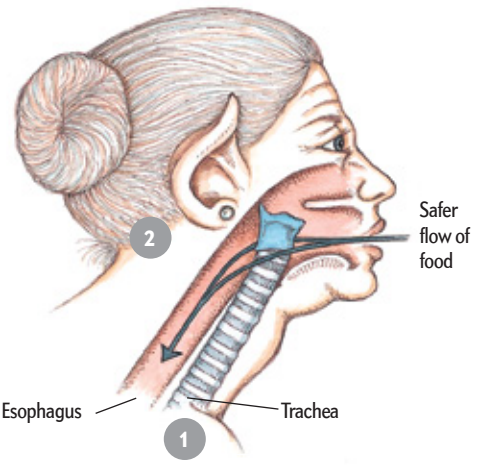
Hair cells of the inner ear, which relay sound information to the brain, become damaged by exposure to loud noises



3 Weak Link between Retina and Back of Eye

This frail connection exists in part because the optic nerve, which carries visual signals from the retina to the brain, connects to the retina only from the inside of the eye, not from the back

FIXES

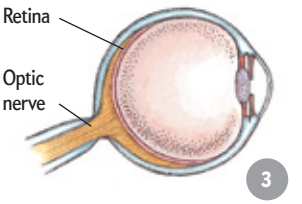


1 Raised Trachea

Would help food and drink to bypass the windpipe more effectively. This design would need refining, though, because it would disrupt breathing through the mouth and the ability to speak

2 Enlarged, Mobile Outer Ear

Would collect sound with greater efficiency, to compensate for internal breakdowns. More plentiful and durable hair cells would preserve hearing longer



3 Optic Nerve Attached to *Back* of Retina

Might stabilize the retina's connection to the back of the eye, helping to prevent retinal detachment

us that undesirable consequences invariably arise whenever humans have taken over the reins of evolution to modify organisms (microbes, plants and animals) to suit their purposes. The most worrisome trade-off for genetic manipulation directed toward living longer would be an extension of frailty and disability rather than an extension of youthful health and vitality.

Though cobbled together by the blind eye of evolution, humans have proved to be a remarkably successful species. We have outcompeted almost every organism that we have encountered, with the notable exception of microbes. We have blanketed the earth and even walked on the moon. We have even figured out how to escape premature death and survive to old age.

At this point in history, we need to exploit our expanding knowledge of evolution to enhance the quality of our lives as we grow older because the single-minded pursuit of life extension without considering health extension could be disastrous.

Our fanciful designs of anatomically "fixed" humans are not intended as a realistic exercise in biomechanical engineering. Given what is known today about human aging, if the task of designing a healthy, long-lived human from scratch were given to a team comprising the father of evolution, Charles Darwin, the great painter Michelangelo, and the master engineer and scientist Leonardo da Vinci, they most certainly would have fashioned a living machine that differs from the one we now occupy. Indeed, anyone who tries his hand at redesign would probably construct a human body that would look unlike the ones we have created on these pages. Yet we invoke this approach as an instructive way of communicating the important message from

© 2015 Scientific American

ANATOMY LESSON 3

Call a Plumber

An experienced plumber looking at the anatomy of a man's prostate might suspect the work of a young apprentice because the urethra, the tube leading from the bladder, passes straight through the inside of the gland. This configuration may have as yet unknown benefits, but it eventually causes urinary problems in many men, including weak flow and a frequent need to urinate.

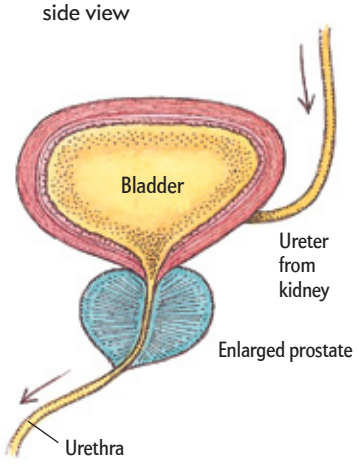
Women also cope with plumbing problems as they age, particularly incontinence. Both sexes could have been spared much discomfort if evolution had made some simple modifications in anatomical design.

MALE PROSTATE
side view

FLAW

Urethra Prone to Constriction

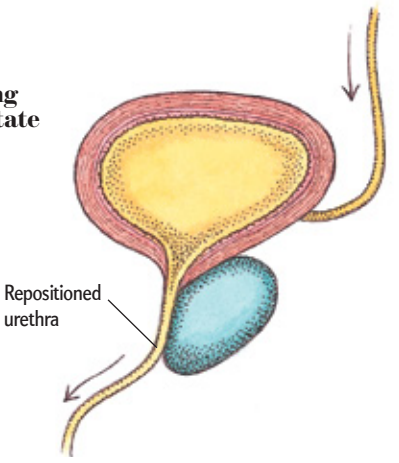
The prostate becomes enlarged in one of every two males at some point in life. As it grows, it squeezes the urethra, potentially obstructing the flow of urine. Total obstruction can be fatal



FIX

Urethra Hugging Outside of Prostate

Would not be squeezed if the prostate became enlarged

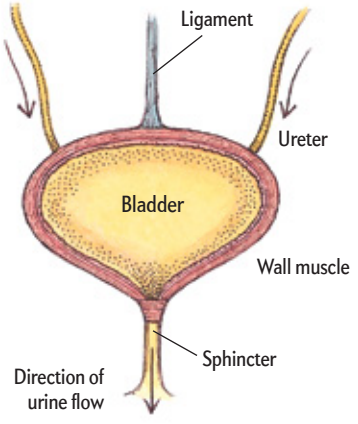


FEMALE BLADDER
front view

FLAW

Muscles and Ligaments That Weaken with Time

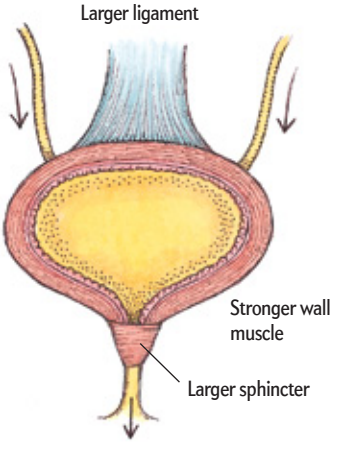
Particularly after multiple pregnancies, the muscles of the pelvic floor and the bladder, and the ligaments that support the bladder, can sag, leading to incontinence



FIX

Stronger Sphincter Muscles in Bladder and More Durable Ligaments

Would increase control over bladder function



evolutionary theory that, to a significant degree, the potential length of our lives and, to a lesser degree, the duration of health and vitality are genetic legacies from our ancient ancestors, who needed to mature quickly to produce children before they were killed by the hostile forces of nature.

S. Jay Olshansky, Bruce A. Carnes and the late **Robert N. Butler** shared an enduring interest in the processes that underlie human aging. Olshansky is professor in the School of Public Health at the University of Illinois at Chicago. Carnes is professor in the Donald W. Reynolds Department of Geriatric Medicine at the University of Oklahoma Health Sciences Center. Olshansky and Carnes collaborate on studies—funded by the MacArthur Foundation, the National Institute on Aging and NASA—of the biodemography of aging (examining the biological reasons for age-related patterns of disease and death in populations). They are co-authors of *The Quest for Immortality: Science at the Frontiers of Aging* (W. W. Norton, 2001).

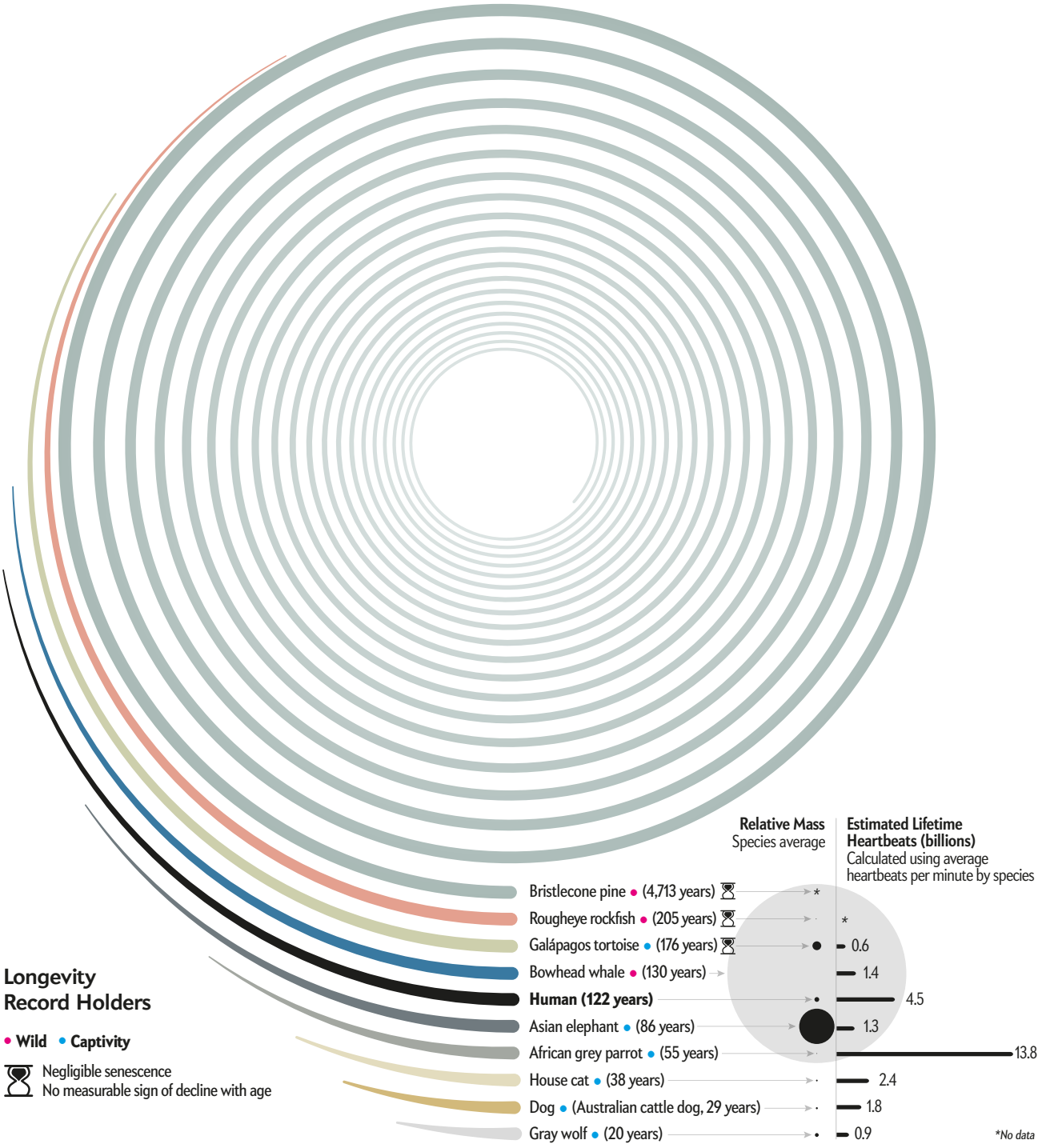
Butler, who died in 2010, was president of the International Longevity Center in New York City and founding director of the National Institute on Aging.

MORE TO EXPLORE

Aging: A Natural History. Robert E. Ricklefs and Caleb E. Finch. Scientific American Library, W. H. Freeman, 1995.
Cheating Time: Science, Sex, and Aging. Roger Gosden. W. H. Freeman, 1996.
A Means to an End: The Biological Basis of Aging and Death. William R. Clark. Oxford University Press, 1999.
Aging: The Paradox of Life. Robin Holliday. Springer, 2007.
How Long Must Humans Live? Bruce A. Carnes and T. M. Witten in *Journals of Gerontology: Biological Sciences*, Vol. 69, No. 8, pages 965–970; August 2014.

scientificamerican.com/magazine/sa

© 2015 Scientific American



WHICH CREATURES LIVE THE LONGEST?

The key indicator for animals may be total energy expended over a lifetime

Conventional wisdom used to be that the life span of a creature was roughly proportional to its body mass and heart rate—the big, slow elephant outlives the quick, small mouse. New research, however, presents a more complicated picture. Bats and birds, for instance, are small but tend to live longer than many larger creatures. Moreover, when scientists look within particular species, size does not correlate well with longevity, although fast growth is often associated with shorter life. To some degree, resting metabolic rate does correlate, but for animals total energy expended over a lifetime may be the best indicator of all. Definitive answers in this field can be slow in coming, partly because the studies take a long time to do—a typical Galápagos tortoise, for instance, can outlast a scientist's career. And don't hold your breath for insights into the extreme life span of the bristlecone pine. *—Fred Guterl*

RECORD-HOLDER SOURCES: JOÃO PEDRO DE MAGALHÃES *AnAge* online database, Institute of Integrative Biology, University of Liverpool; "PATENTED HARPOON PINS DOWN WHALE AGE," BY AMANDA LEIGH HAAG, IN *NATURE*, PUBLISHED ONLINE JUNE 19, 2007 (*whale*); GUINNESSWORLDRECORDS.COM (*dog and elephant*); *GUINNESS WORLD RECORDS 2010* (*cat*); *THE TELEGRAPH*, JANUARY 6, 2015 (*parrot*)

Research and Graphic by Graphicacy

© 2015 Scientific American

AARP Real Possibilities with

Staying Sharp

WHAT HAVE YOU DONE FOR YOUR **BRAIN** TODAY?

Learning More is just one of the five pillars of AARP's holistic approach to brain health. The Staying Sharp membership helps you challenge your brain in new ways every day. As a member, you'll get access to eNewsletters and videos to keep you updated on the latest research, as well as a series of online brain exercises developed by neuroscientists specifically for AARP members.

Join now at **aarp.org/joinstayingsharp**

AARP Real Possibilities with

Staying Sharp

Keep your mind active and healthy so you can **Shine On.**

The AARP Staying Sharp membership positively challenges and stimulates the brain. It offers a uniquely holistic approach, addressing the five pillars of brain health: Keeping Fit, Learning More, Managing Stress, Eating Right and Being Social. Through information, tools, and tips, you'll be able to stay informed and in control, so you can truly shine.

STAYING SHARP MEMBERSHIP **$21.00** / YEAR

***Just $5** more than traditional membership!*

Join now at **aarp.org/joinstayingsharp**